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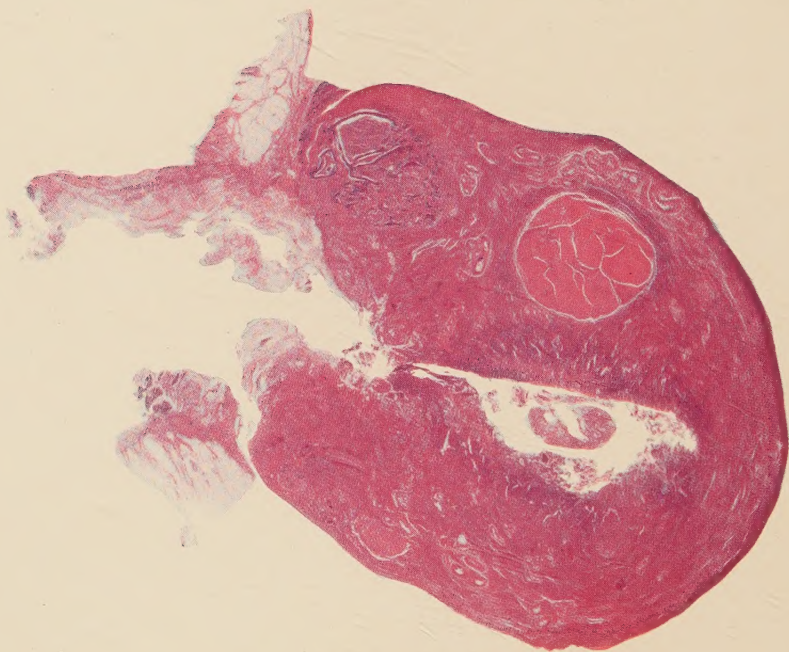
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A MYOMATOUS UTERUS THE SEAT OF AN ADVANCED CERVICAL CARCINOMA. The carcinoma involves the entire upper third of the vagina, the cervix was replaced by a carcinomatous ulcer. Treated with radons. Complete local healing and cessation of bleeding and discharge. The more distant carcinoma continued to advance, and death ultimately resulted from pressure upon the uterus. This case demonstrates the value of small doses of emanation for certain advanced cases of cervical carcinoma.

RADIUM IN GYNECOLOGY

BY

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WITH A CHAPTER ON PHYSICS BY

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49 ILLUSTRATIONS



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PREFACE

THE action of radium and the X-ray upon living tissue are in many respects similar. In the treatment of some conditions a combination of both methods can be employed with advantage. For this reason, references to X-ray therapy have been incorporated in the present work.

Radium was discovered by Madame Curie in 1898. Necessarily, a certain time elapsed before sufficient radium was available for anything like general use. Despite the short period during which this element has been employed as a therapeutic agent, a vast literature has arisen. Many unsolved problems in relation to radium therapy still exist, and this and the divergent views regarding its efficacy in the treatment of many of the gynecological conditions for which it has been employed have made the selection of the literature extremely difficult.

Those who attempt to employ radium therapy with insufficient knowledge and experience are likely to do much harm, as are those who treat malignant neoplasms without having a sufficient quantity of radium available. One of America's foremost surgeons has epigrammatically remarked that ten cents' worth of radium may do a million dollars' worth of injury.

Accuracy in diagnosis is essential to the successful application of radium therapy. This has led us to repeatedly stress the warning that radium should only be used by those capable of making an accurate pelvic diagnosis. Radium therapy in gynecology is essentially the handmaiden of the surgeon. Its status in the treatment of many conditions is

definitely established. In the treatment of properly selected cases of benign uterine hemorrhage, irradiation stands alone, the almost complete absence of mortality and morbidity and the practical certainty of cures which result, far surpass any operative results or any other form of therapy. Despite the fact that it is not yet known with certainty how radium affects carcinoma, it is proven that certain types may be destroyed by irradiation as surely as with the knife or cautery and, in some cases, more readily and with less mortality and morbidity. The problem is not, will radium cure carcinoma, but, can sufficient dosage be applied to the cancer cells. Further studies, especially pertaining to end-results and a correlation with histologic types of cancer, are urgently required. Uniformity in methods of computing statistics and careful elimination of undue enthusiasm are necessary. With cancers of certain localities no satisfactory method of treatment is available, and the physician and surgeon are forced to employ that which offers the best hope of cure in the individual case. It is to be hoped that the day will come in which the dread disease can be attacked from a more logical and scientific standpoint than is possible at present.

Scherechewsky states that the death rate from cancer of the female genital organs rose enormously during the twenty years following 1900. Whether this is an actual increase or due to more accurate methods of diagnosis and that the average age of the population is increasing, resulting in a greater percentage of persons reaching the cancer age, and to other causes, is a matter of opinion, but the undoubted fact that cancer is one of the greatest factors in the production of mortality among persons over forty years of age is certain. Maude Slye and others have apparently demonstrated the heredity tendency which exists towards cancer

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among animals. T. C. Wood believes that heredity plays little or no part in the development of cancer in man, and, from a practical standpoint, this appears sound reasoning. There are probably few persons who have not had one or more progenitors affected with this disease.

Since the inception of this work, unforeseen conditions have arisen which have prevented the full coöperation of the senior author. If this had not been the case, many of the faults of omission and commission which are present in this monograph would have been eliminated.

CHARLES C. NORRIS.

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RADIUM
IN GYNECOLOGY

RADIUM IN GYNECOLOGY

CHAPTER I

HISTORIC*

HISTORICAL.—About the middle of the last century several German physicists were investigating the passage of electricity through rarefied gases. For this purpose they used glass tubes or bulbs of various shapes with metal electrodes, known in Continental Europe as Hittorf tubes. A little later English physicists took up the work and, under the leadership of Crookes, made further developments. The beautiful luminescence produced in the rarefied gases of the tubes by the passage of electricity, was partly responsible for the attention which this work attracted. On the other hand, the leading physicists of the latter part of the nineteenth century, such as Helmholtz and Lord Kelvin, believed that the explanation of the phenomenon would prove of great scientific value. This was the “setting” when Roentgen took up the work which culminated in the epoch-making discovery of X-rays.

The announcement of this discovery in December, 1895, created a sensation in the scientific world, and a great many physicists undertook to duplicate Roentgen’s experiments. This gave a tremendous impetus to the study of the new

* This chapter written in conjunction with Gioacchino Failla, D.Sc.

phenomenon as well as the new type of radiation, and led to another momentous discovery.

Roentgen had pointed out that the X-rays appeared to emanate from the part of the vacuum tube which, under the action of the applied voltage, fluoresced most brilliantly. This was confirmed by other investigators and a close association between fluorescence and X-rays was surmised. We know now that the fluorescence of the glass in Roentgen's tubes was only incidental and is not essential to the production of X-rays, but the erroneous inference proved most fruitful. Working on this hypothesis, Henri Becquerel experimented with numerous substances which were then known to be strongly fluorescent, to see whether X-rays were associated with the luminescence. He placed the substances under investigation upon a photographic plate, which had been wrapped in black paper, and exposed it to sunlight. This caused the mineral to fluoresce, and, if penetrating rays like X-rays were produced simultaneously, they would affect the photographic plate.

Among the substances tested were some uranium compounds, and Becquerel found that these did affect the photographic plate. In accordance with his original hypothesis he supposed that the rays which penetrated the black paper were emitted by the material under the action of sunlight. However a little later he discovered accidentally that sunlight was not essential for the manifestation of this effect. Further experiments soon convinced Becquerel that the emission of the penetrating radiation was a property of the uranium compounds. Thus the phenomenon of *radio-activity** came to be discovered (1896).

The announcement of the discovery of radio-activity in

* This name was really suggested later by Mme. Curie.

1896 suggested to the Curies a promising field of investigation and Mme. Curie took up the work immediately. At that time it was already known that X-rays ionized gases and that uranium rays had the same property. Ionization furnished a better means of making quantitative studies of radio-active minerals and so this method was adopted. Pierre Curie in his work on piezoelectricity, in conjunction with his brother Jacques, had developed a sensitive electrometer. To this had been added an ingenious device based on the piezoelectric property of some quartz crystals, and the combination formed an excellent instrument for the measurement of small ionization currents. With this equipment Mme. Curie studied the activity of uranium compounds, and found that it depended solely on the amount of uranium present in the material. This work led to the conclusion that radio-activity was an atomic phenomenon and was independent of the chemical combination of uranium and of external conditions. The importance of this result cannot be over-estimated for it was really responsible for the discovery of radium, as we shall see presently.

Having found that uranium was a radio-active element, the most logical step was to see whether the same property was exhibited by some other chemical element. All the known elements, therefore, were tested by Mme. Curie, and she found that thorium* was the only other radio-active substance. In the course of this work Mme. Curie had tested some uranium minerals which were considerably more radio-active than pure uranium or thorium. Knowing from the work already mentioned that the activity of uranium was not influenced by chemical or physical conditions, Mme.

*Independently Schmidt discovered the radio-activity of thorium at about the same time.

Curie concluded that there must be in the mineral some other element more active than uranium or thorium. But since all known elements had been found to be non-radio-active, this must be a new element. Ordinary chemical analysis did not reveal this element, hence it must be present in very minute quantities and must be strongly radio-active. This vision appeared to the Curies and stirred their imagination. Pierre Curie dropped his experiments on the growth of crystals and joined Mme. Curie in the fascinating search of the unknown element.

The work was greatly facilitated by the radio-active property of the material under investigation. This made possible the tracing of very minute quantities of the substance through a series of chemical transformations, by simply measuring the activity of the separate products of the chemical analysis. Pitchblende, the uranium ore which the Curies undertook to analyze, showed an activity about four times as large as that of pure uranium oxide. Some of the products of the chemical separation showed a greater activity, and it soon became evident that the mineral contained at least two new radio-active elements, closely allied to bismuth and barium respectively. As the chemical separation progressed, the activity of the two main products increased, becoming several hundred times larger than that of uranium. Then from the bismuth group, polonium was identified as a new chemical element and was named after Mme. Curie's native country (July, 1898). The barium group yielded even more striking results. As the activity increased the mean atomic weight of the mixture became larger than the atomic weight of barium. By carrying out further the fractional crystallization a still more active material was obtained which was phosphorescent. Finally a new chemical element

was definitely identified and it was aptly named "Radium" on account of its great radio-active power. The first announcement relating to this new element was made on the 26th of December, 1898, in a short paper by M. and Mme Curie and Bemont, read before the Academy of Sciences of Paris.

Mme. Curie continued her work on the chemical separation of radium, and in 1902 obtained 100 milligrams of practically pure radium chloride. A larger quantity had been obtained by 1907 and this permitted an accurate determination of the atomic weight of the element. Metallic radium was later produced by Mme. Curie and Debierne.

To appreciate the magnitude of the laborious process of extracting radium it should be remembered that one ton of the best pitchblende contains much less than one gram of radium. That is, radium is present in the ore in the ratio of one to several million. This gives also an idea of the extreme delicacy of the ionization method employed in tracing the radio-active material along the different steps of the chemical analysis.

Like the discovery of X-rays, the identification of strongly radio-active substances created a sensation in the scientific world. Many chemists and physicists were anxious to work with the new elements and a world-wide search for radio-active minerals was on. But these minerals were very scarce and the process of extraction of the radio-active constituents not simple. The Curies had interested Arnet de Lisle in the commercial production of radium and small quantities of rather impure radium salts were soon purchasable. Later, salts of high purity were also available, but for the small quantities obtainable the price in 1904 was at the rate of 160,000 dollars per gram of radium element. Doctor Giesel of the *Chimiefabrik*, Braunschweig, deserves

special mention here for having been the first to put on the market practically pure radium salts, which were sold at a very reasonable price. Many institutions were thus able to secure the coveted materials, with incalculable benefit to the science of radio-activity.

The ore from which Mme. Curie extracted the first radium came from Joachimsthal in Bohemia, then a part of the Austrian Empire. On account of the limited quantity available and the great demand for it, the Austrian Government prohibited the exportation of pitchblende. Considerable quantities of radium were then extracted in Austria, the largest amount going to the Radium Institute of Vienna. This institute differs from those of a later date, founded in different countries, in that the work is restricted to the study of the chemical and physical properties of radio-active substances. The Austrian embargo on pitchblende led to the extraction of radium from poorer ores in different parts of the world. Among these, carnotite from Colorado played an important part and for several years large shipments were made to Germany, England, and France. Radium was not produced commercially in the United States until 1913. After this date, however, the industry grew rapidly and this country supplied practically all the radium sold.

In one way or another, soon after the discovery of radium, many laboratories secured small amounts of radium or other radio-active substances. Intensive experimentation started and important discoveries were made in different countries. To France belongs the honor of the discovery of the radio-active elements, but the British Empire gets a large share of the credit for the scientific development of radio-activity. The brilliant work of Rutherford laid a solid foundation for such development. In 1902-1903 Rutherford and Soddy

worked out the theory of successive transformations of radio-active elements, and this, as it were "put the house in order." Other distinguished British scientists, too numerous to mention, made also very important contributions to this field. The Nobel prize for 1908 was awarded to Rutherford. It should be added here, however, that the rapid development of the new science was due to the world wide interest which radio-activity elicited. Important contributions were made in other countries besides France and the British Empire. In Germany particular attention was paid to the thorium series of radio-active elements.

MME. CURIE.—In 1898 Mme. Curie discovered radium. Prior to this, and working in the laboratory of M. Curie, much painstaking work was done. The amount of radium that could be isolated from any given ore was infinitesimal, and the process of isolation was extremely laborious. At first only 0.1 gr. was obtained from two tons of uranium, but later Giesel¹ succeeded in extracting four grains from one ton of pitchblende that came from the Joachimsthal Mine in Bohemia. The Austrian Government aided Mme. Curie very materially by supplying her with several tons of pitchblende.

In 1900 Debierne demonstrated a radio-active product of pitchblende which he called "Actinium," and in 1905 Hahn² isolated radium, thorium, and mesothorium. In 1907 Boltwood³ discovered "Ionium." At the present time some 30 or 40 radio-active substances are known.

Radium emits three different types of rays, namely, the Alpha, Beta, and Gamma rays, which differ in their penetrating powers. According to Forsdike,⁴ the principle of filtration was introduced by Wicham, Degrais, and Dominici, with the object of absorbing the weaker penetrating rays in

order to prevent injuries to the superficial structures, and at the same time deliver an adequate dosage to the deeper tissues. Thus, if it were not for screening, the superficial tissues would be exposed to much greater irradiation than would the deeper tissues. Various metals have been employed for screening purposes, lead, silver, gold, and platinum being among those most frequently utilized.

Mme. Curie, as has been stated, is of Polish birth, having been born in Warsaw on November 7, 1867. Both her father and mother came from the small Polish landed proprietors. Her grandfather divided his time between agriculture and directing the affairs of a provincial college. Her father studied at the University of Petrograd, and later became professor of physics and mathematics at Warsaw. He was interested in literature and was well acquainted with Polish poetry, as well as with that of other lands, a characteristic inherited by his gifted daughter. Mme. Curie's mother, Mme. Skłodowska, was younger than her husband, was well educated, and at the time of her marriage was a director in a school for young girls at Warsaw. She was a musician and singer. Mme. Curie's father and mother were studious to a marked degree.

Mme. Curie's maiden name was Marie Skłodowska. She was one of five children. An elder sister died, leaving two sisters and a brother. Her mother died at the age of forty-two, when the child, Marie Skłodowska, was nine years of age. Both parents were Catholics. Marie Skłodowska's education began at the age of six; she was the smallest girl in her class, and was frequently called upon to recite. Because of her diffidence, this was a great trial to her. She early showed a tendency toward mathematics and physics. At fifteen she completed the high-school course, having taken

first rank in all her studies. At seventeen, she left home to begin an independent life, having accepted a position as governess. This position she held for three and a half years, after which she returned to Warsaw, where a similar position awaited her. She remained in this new position for one year and then went back to her father, who had retired and was living alone. During the year that followed, she continued to educate herself.

To her great joy, for the first time in her life she was permitted to have access to a small municipal physical laboratory, directed by one of her cousins. Here, however, she found little time for work except during the evenings and on Sundays. A sister had gone to Paris to study medicine and had married there, and in November, 1891, at the age of twenty-four, Marie Skłodowska went to Paris to live with her sister and to pursue her studies further. This arrangement, however, did not prove satisfactory owing to the distance of the home from the schools. Finally she secured a modest room near the centre of her studies. Because of her limited means, her living conditions were far from luxurious. The room she occupied was in a garret and was very cold in winter. Here, with the aid of an alcohol lamp and a few kitchen utensils, she prepared her meals. These were often limited to a cup of chocolate, eggs, or fruit.

She performed all her household duties herself, carrying the coal she used up six flights of stairs. In this room she often worked until late at night. In demeanor she was reserved and shy, but it was not long before she made friends with her instructors and her fellow-students. Her preliminary teaching had been deficient, but she quickly overcame this handicap, and in 1893 she had the satisfaction of graduating in first rank as "*Licenciée ès Sciences Physiques*," and

second in rank as "Licenciée ès Science Mathématiques" in 1894. In the latter year, while studying at the Sorbonne, she met her future husband, Pierre Curie.

Pierre Curie was born in Paris, May 15, 1859, being eight years older than Mme. Curie. His father and grandfather were physicians. Pierre received his Licentiate in Physical Science at the age of eighteen. At an early age he began work in the School of Physics, first as director and later as professor for practically the whole of his scientific life. Like many scientists, he was a man of small means and, as a result he was greatly handicapped in his studies.

The couple were married in July, 1895. The wedding was a very simple one, the bride wearing her usual day dress. At the time of her marriage one of Mme. Curie's relatives gave her a gift of money to be used for the purchase of a trousseau; while not a great sum, it meant much to the poor student. To understand the significance of the use to which she put the fund it is necessary to remember that Marie Sklodowska was young and possessed beauty and charm. Instead of a trousseau, she purchased two bicycles, in order that she and Pierre might enjoy the country on their honeymoon. Pierre Curie's salary then was about \$100 a month. He was thirty-six years old at this time and had just been made professor in the School of Physics and Chemistry of the city of Paris.

Mme. Curie was preparing to take the examination with the aggregation of young women with a view to obtaining a teaching position. The young couple lived a very simple life, working out their laboratory experiments and teaching requirements. All formal social obligations were excluded. During a period of eleven years they were scarcely ever separated, so that very few letters passed between them dur-

ing that time. In August, 1896, Mme. Curie was awarded first position in her examination.

In September, 1897, a daughter, Irene, was born. The living apartment was located near the school in order that little time would be lost in transit.

The young couple's resources were limited, and Mme. Curie attended to the housekeeping and the preparation of the meals. With the exception of a few trips and short excursions to the neighboring country on their bicycles the Curies devoted practically all their lives to the furtherance of scientific work.

Professor Curie gave much care to the preparation of his courses, and in this Mme. Curie assisted him. Most of their time, however, was devoted to research. Neither of them had a private laboratory, but utilized a corner of the Physics School building.

About this time Mme. Curie undertook an investigation of the magnetic properties of steel, a work that was published in 1897. In the meantime the problem of taking care of little Irene and of the home without giving up scientific work loomed large. The Curies saw but few friends, most of these being scientific workers.

It was toward the end of 1897, and while living in this quiet way, that the work which ended in the discovery of radium was begun. Mme. Curie's interest had been directed to Henri Becquerel's experiments with the salts of uranium. As was previously stated, Becquerel had shown that uranium affected a photographic plate in the same way as if it had been exposed to light. At first Becquerel believed that this effect was the result of exposing the uranium salt to light, but it was later discovered that this was not the case.

Mme. Curie resolved to undertake a special study of the

phenomenon, and decided that the first step should consist of making precise measurements. To do this she utilized the property of the rays that enabled them to discharge an electroscope. One of the models of the first apparatus employed for this purpose is now in the College of Physicians in Philadelphia.

Various minerals were tested; some of these were found to possess an activity three or four times greater than that of uranium. Mme. Curie did not expect, even at the beginning, to find a new element in any large quantity, as all the minerals had already been analyzed with precision. She believed, however, that there might be as much as 1 per cent. of some unknown substance present. However, as the research progressed, it became clearer that the new radio-active element could exist only in very minute proportions and that, in consequence, its activity must be very great. As a matter of fact, it was only after several years of arduous labor that she finally succeeded in completely separating the new substance, which is now known as radium. The following story is told in Mme. Curie's own words:

"We did not know, at the beginning, any of the chemical properties of the unknown substance, only that it emits rays and it was by these rays that we had to search. We first undertook the analysis of a pitchblende from St. Joachimsthal. Analyzing this ore by the usual chemical method, we added an examination of its different parts for radio-activity by the use of our delicate electrical apparatus. This was the foundation of a new method of chemical analysis, which, following our work, had been extended, with the result that a large number of radio-active elements have been discovered. In a few weeks we became convinced that our prevision had been correct, for the activity was concentrating in a regular

way, and in a few months we could separate from pitchblende a substance accompanying the bismuth, much more active than uranium, and having well-defined chemical properties.

“In July, 1898, we announced the existence of this substance, to which I gave the name of Polonium, in memory of my native country. While engaged in this work we had also discovered that, accompanying the barium separated from the pitchblende, there was another new element. After several months of close work we were able to separate this second new substance, which was afterward shown to be much more important than Polonium. In December, 1898, we could announce the discovery of this new and now famous element, to which we gave the name of radium. It was chiefly by the radiant properties that this new substance was distinguished from bismuth and barium, with which they were mixed in minute quantities. It was necessary to separate them as pure elements. We were poorly equipped.

“It was necessary to subject large quantities of ore to careful chemical treatment. We had no money, no suitable laboratory, and no permanent help. We knew by our experiments that, in the treatment of pitchblende at the uranium plant in St. Joachimsthal, radium must have been left in the residues. We succeeded in securing a small quantity of these residues. The activity of the residues proved even greater than of the primitive ore. Some time later the Austrian Government, on the proposition of the Academy of Sciences of Vienna, let us have several tons of similar residues at a low price. The School of Physics could give us no suitable premises, but for lack of anything better the director permitted us to use an abandoned shed which had been in service as a dissecting room. The roof leaked, the room was suffocating in summer and bitter cold in winter. One of our joys was to

go into our workroom at night; we then perceived on all sides the feebly luminous silhouettes of the bottles containing our products. It was really a lovely sight and one always new. The glossy tubes looked like fairy lights. It was only after treating an entire ton of pitchblende residues that definite results were obtained."

In 1900 Mme. Curie was made professor at the Normal Superior School at Sèvres. In 1903 she finished her doctor's thesis and obtained her degree. At the end of the same year, the Nobel prize was awarded jointly to Mme. Curie, Pierre Curie, and H. Becquerel. The prize was a great help to Mme. Curie in the continuation of her research work.

In 1904 a second daughter, Eva Denise, was born, who has since become an accomplished musician. In 1906 Professor Curie was struck by a motor and killed. Shortly after this the Faculty of Sciences of Paris offered Mme. Curie the chair left vacant by her husband's death. In the same year she began to teach in the Sorbonne as associate professor, and two years later she was named titular professor.

In 1907 Mr. Andrew Carnegie donated a sum, the annual income of which was to be used for research fellowship in Mme. Curie's laboratory. In 1910 Mme. Curie was able to achieve a new determination of the atomic weight of radium, and in the same year she isolated the metal. The latter operation, an extremely delicate one, has never been repeated, since it is accompanied by the serious danger of loss of radium.

Mme. Curie devised a method for determining the quantity of radium present in a substance by means of a radio-active gas produced by it and called this "Emanation."

The first experiments to determine the biologic properties of radium were made in France from samples obtained from

the Curie laboratory. These were so encouraging that a new branch of medicine, namely, radium therapy (in France called Curietherapy), became established.

In 1910, in spite of the insistence of the ministry, Mme. Curie refused the decoration of the Legion of Honor, giving as her reason that her husband had been opposed to all honorary distinction. In the same year Mme. Curie's candidacy for the Academy of Sciences, for which she had been persuaded to become an applicant, was refused. In 1911 she received the Nobel prize. In 1912, while slowly recovering from an illness, the creation of an Institute of Radium was begun, but for lack of financial support this was not completed in 1914 when the war began.

When the danger of the German attack on Paris became pressing, the supply of radium was taken to Bordeaux. During the war Mme. Curie organized radiologic and radio-therapeutic services for the military hospitals. The numerous new hospitals that were established throughout France in the first months of the war were, as a rule, without X-ray facilities. To meet this emergency Mme. Curie gathered all the apparatus she could find in the laboratories and stores, and with this equipment, in August and September, 1914, she established several stations. As the need for more apparatus became greater, she equipped a Red Cross radiologic car. This mobile station enabled radium treatment to be given in many hospitals that were without other means of supplying this requirement.

Mme. Curie made several journeys to the army zone. She was assisted in her work by her daughter Irene. At Mme. Curie's suggestion, and with her aid, a department of radiology was founded at the Edith Cavell Hospital, and a course was organized at the Radium Institute that provided

training for 150 operators. Mme. Curie also found time to write a small book entitled "Radiology and the War."

Emanations were furnished to the Health Service from the Radium Institute. Having no assistants, Mme. Curie herself, without aid, for a long time prepared these emanations. During the summer of 1918, at the request of the Italian Government, Mme. Curie visited Italy in order to study the mineral resources of that country with a view to determining the radio-activity of the minerals found there. In 1921, at the suggestion of Mrs. Meloney, editor of the "Delineator," a fund was raised by the women of America with which to purchase one gram of radium. Mme. Curie and her daughter visited the United States and the radium was presented to her by President Harding at the White House.

During her short visit to the United States many honors were conferred upon the discoverer of radium. Mme. Curie has scrupulously avoided accepting any material profit as the result of her discoveries. No patents have ever been applied for, and the radium that she extracted was donated to the Radium Institute. A characteristic incident is related by Mrs. Meloney: "On the night before the reception at the White House, at which President Harding was to present the gram of radium to Mme. Curie, a deed of gift was taken to her. It was an engraved scroll, vesting all right to the gram of radium (\$100,000 worth) to Marie Curie.

"She read the deed carefully and said: 'It is very fine and generous, but it must not be left this way. The gram of radium represents a great deal of money, but more, it represents the women of this country. It is not for me—it is for science. I am not well, I may die any day; my daughter Eva is not of age, and if I should die it would mean that the radium would go to my estate and would be divided. This

radium must be consecrated to science.' When told that the deed could be altered within a few days she was dissatisfied, fearing that too much was at stake, and the deed was altered the same night."

Most of the foregoing material has been procured from the book "Pierre Curie," written by his wife, Marie Curie, New York, 1923. This volume and the autobiographical notes do not do Mme. Curie justice, and it is only by reading between the lines that the fine character, wonderful mind, and brilliant research qualities of the author can even be guessed at. Mme. Curie is of a simple, retiring nature, fond of flowers, always practising self-effacement, and it is related that it was only with the greatest difficulty that she was persuaded to write the aforementioned volume.

Under what difficulty she worked, and with what persistence her researches were carried on, despite the handicaps of ill health, limited means, the rearing of a family, and the loss of a husband, is hardly conceivable. Working all day in her makeshift laboratory, stirring huge cauldrons of molten metal with a heavy iron bar, returning exhausted to her home to prepare the family meal, and often resuming her labors in the laboratory at night—these give but a glimpse of the arduous task she set for herself, but which, after years of the hardest labor, finally resulted in the discovery of radium.

FIRST USED.—Radium was first used in the treatment of uterine hemorrhage due to benign lesions by Oudin and Verchire.⁵ These writers introduced 11 mgm. of radium into the uterine cavity for 15 minutes, repeating the treatment five or six times at intervals of four or five days. The radium was in a glass container and it is probably due to this fact that considerable local reaction resulted.

Kelly⁶ gives Cheron⁷ the credit for being the first to secure positive results from radium treatment in these conditions. Cheron reported his technique and results to the Academie de Medicine in 1909. He employed 30 mgm. of radium in a glass tube and a O. S. mgm. filler of silver. This was inserted either into the uterine cavity or into the cervical canal. The treatment lasted for from six to eight hours, being repeated at intervals of a few weeks, the total dosage being 2160 milligram hours.

In this series 120 women suffering from small uterine myomata were subjected to treatment, amenorrhea resulting in 117 and shrinkage of the tumor in 108. In 1906 Robert Abbé⁸ reported treating one case, and more recently the same investigator⁹ reported two others treated years before, with good results. In 1912 Pinch¹⁰ treated two patients at the Radium Institute in London, with good results. Gauss and Krinski,¹¹ who had formerly employed the X-ray in the treatment of these cases, recorded their results with mesothorium, amenorrhea being secured in all cases.

Early in the history of radium Dr. Howard A. Kelly, who has done so much for the science of gynecology, recognized the value of this agent in the treatment of various diseases of the female genital tract, and it is largely owing to his vigorous pioneer work that radium therapy was so quickly recognized in America as well as abroad. Kelly insisted upon the intra-uterine rather than the intracervical application of radium in the treatment of myomata, and in 1914, together with Burnam,¹² reported excellent results in a series of cases of hemorrhage of benign origin that had been treated for one or two years. To Kelly also belongs a large part of the credit for developing the irradiation treatment of carcinomata of the female genital tract.

In 1908 Duane¹³ first suggested the use of emanation directly within the carcinomatous growth. Some years later Joly and Stevenson¹⁴ reported a series of cases treated in this manner. To Janeway,¹⁵ however, is due largely the credit for perfecting the technique. He was the first to utilize emanation as a prophylactic agent following the dissection of lymphatic structures at a distance from the primary tumor. In 1919 he reported the results secured in the treatment of five cases of vulvar carcinoma treated by emanation and dental compound.

Owing to its frequency, accessibility, histologic structure, and the unsatisfactory results secured by surgery in its treatment, carcinoma of the cervix was one of the earliest forms of malignant neoplasm subjected to radiotherapy. Radium having been discovered in France, it is only natural that it should have been first employed in that country. As Muir states, the history of radiotherapy of cervical cancer is the history of radiotherapy itself. The X-ray was discovered in Germany and to these two countries belong much of the credit for the pioneer work in irradiation for cervical carcinoma. In 1913 the Middlesex Hospital sent two representatives to Paris to investigate the merits of radium in the treatment of cancer. As a result this institution secured 435 milligrams of radium bromide and subsequently reported favorably on its use. In 1915 Kelly and Burnam reported their work with radium before the American Gynecological Society and the American Medical Association.

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CHAPTER II

THE PHYSICS OF RADIUM

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COMMERCIAL PRODUCTION OF RADIUM.—It is an interesting coincidence that soon after the announcement in France of the discovery of radium, two Frenchmen, C. Friedel and E. Cumenge, described a radium-bearing ore found in Colorado. This material was first analyzed by Marie Adolph Carnot, Director of the Ecole des Mines of Paris, and is therefore called carnotite. Its radium content is much lower than that of pitchblende, from which radium was first extracted, and besides it is generally mixed with other minerals. Ores rich in carnotite have a canary-yellow color and are rather friable. Ordinarily the carnotite forms part of the cementing substance between sand-grains.

Prof. Hamilton Phillips, of Princeton University, procured some carnotite ore in 1902 and obtained some radium concentrate from it in December of the same year. Mr. Stephen T. Lockwood, of Buffalo, formed the Welch-Lofftur Uranium and Rare Metals Company which produced also radium concentrates of considerable activity in 1903. (The products of these early attempts are now in the United States National Museum.) In the meantime Colorado carnotite was being shipped to Europe to supply extraction plants in France, England, and Germany, and some of the radium was then sold in the United States.

In May, 1911, the Standard Chemical Company was organized by Mr. Joseph Flannery of Pittsburgh, to undertake the commercial production of radium from carnotite ore. This company had sufficient resources to make a thorough study of the problem and succeeded in developing a process which was commercially feasible. It produced the first radium of high purity in January, 1913. By 1914 this company was prepared to put on the market one gram of radium a month—a much larger output than any European producer.

The radium treatment of cancer was tried soon after the discovery of the element, but it was after 1910 that the extensive use of this agent began. European producers were unable to supply the demand. The price of radium was very high and its purity often poor. Dr. Howard A. Kelly, of Baltimore, who had bought radium in Europe, obtained some striking results in cancer cases and was very anxious to secure a large supply of the new agent. At about the same time, Dr. James Douglas of New York, a distinguished mining engineer, became interested in the radium treatment of cancer from a philanthropic point of view. The United States Bureau of Mines became interested in radium in 1912, at which time large shipments of carnotite were being made to Europe.

The coincidence of these activities led to the formation of the National Radium Institute by Doctor Kelly and Doctor Douglas to coöperate with the Bureau of Mines in the extraction of radium from carnotite. Under this arrangement Doctor Kelly and Doctor Douglas provided the capital for the erection of the necessary plants in Colorado, the mining of the ore, and the cost of extraction. The Bureau of Mines assumed responsibility for the develop-

ment of a suitable process of extraction and for the technical supervision of the work. The agreement between the National Radium Institute and the Bureau of Mines was approved by the Secretary of the Interior on October 13, 1913. In this it was further stipulated that any radium produced in excess of seven grams of anhydrous radium bromide (RaBr_2) from any 1000 tons of carnotite ore, was to be donated to the Bureau of Mines. The radium delivered to the National Radium Institute was to be divided equally between Doctor Kelly and Doctor Douglas. The latter was interested in developing the treatment of cancer at the Memorial Hospital in New York, and his share of the radium was intended for that institution. Work under this coöperative arrangement was started immediately and the regular production of radium began in June, 1914. By January, 1917, when the agreement expired, about 8.5 grams of radium had been extracted. The results of the work done by the Bureau of Mines in the production of radium were made public in Government bulletins issued from time to time.

As a matter of historical interest we may mention here the Congressional investigation of the radium situation in the United States. In 1912 large quantities of carnotite were being shipped to Europe, while there was a great demand for radium and none was purchasable in this country. The Bureau of Mines made a survey of the radium-bearing lands in Colorado and Utah and reported that only a limited amount of carnotite was available. This started a campaign for the conservation of the valuable ore. When the Standard Chemical Company began to produce American radium early in 1913, the price was over \$120 a milligram, but later it was stabilized at that figure. Radium produced by the

Austrian Government was then being sold at the same price. Many thought at the time that this price was too high, and a considerable sentiment for a Government monopoly of radium developed. The Bureau of Mines, in the meantime, had become actively interested in the extraction of radium through the coöperative arrangement made with the National Radium Institute, and naturally favored the production of radium under Government control. As a result of this general situation bills were introduced into Congress for the purpose of conserving the radium deposits of the country, by withdrawing from entry all public lands containing radium, and to authorize the Bureau of Mines to take charge of the Government production of radium. After lengthy investigations by the House and Senate Committees on Mines and Mining, the bills were dropped and the radium industry was left to develop under private initiative.

We have already mentioned the Standard Chemical Company as the first to put on the market practically pure radium salt extracted in this country from carnotite. This was in January, 1913. About a year later a second concern, the Radium Company of America, of Sellersville, Penn., also produced high purity radium. This company, however, operated only for a short time. Then, after the Congressional investigation was dropped, other radium concerns were organized. The W. L. Cummings Company, of Philadelphia, came next. Later the Radium Company of Colorado entered the field, and after the World War, the Radio Chemical Corporation. This concern was later reorganized as the United States Radium Corporation, with offices in New York and an extraction plant in New Jersey.

All these concerns were engaged primarily in the production of radium for medical uses. They were also engaged,

directly or indirectly, in the manufacture of luminous materials for watch dials, etc. During the war considerable quantities of radium were used for the luminous materials needed for gun sights, airplane instruments, etc. Competition in the medical field became very keen, particularly after the war. The price of radium dropped first to \$110 a milligram, then to \$100. Great stress was put on the "service" which each concern would render to the radium buyer and a lavish distribution of literature, instruments, and applicators was made. Under these conditions the radium industry was not very profitable and some of the concerns decided to liquidate. The process of elimination was accelerated by the appearance on the market of Belgian radium.

Radium ores had been identified in the Belgian Congo as early as 1913 by the technical staff of the Union Minière. At the beginning of the war, however, little had been done toward the exploitation of these minerals. In fact, it was not until some time after the war that active steps were taken. The indirect way in which this came about is rather interesting and we shall quote here from an article which appeared in "*Le Neptune*" of October 16, 1921. Prof. Alfred Schoep, Director of Ghent Institute of Mineralogy, received from time to time mineralogical specimens gathered here and there by his former students. In 1920 among several minerals coming from Katanga, Belgian Congo, he found a piece of pitchblende. Professor Schoep, describing this incident, says—"I did not pay much attention to it, because one must guard against jokers. But the following summer while visiting the British Museum at South Kensington, its learned Curator, Doctor Spencer, showed me his recent acquisitions. Among these, to my surprise, I found an ore exactly similar to the one which I had received from

Katanga a few months before. A still more curious thing happened. In the case from which this specimen was taken I found another mineral of a yellow ochre color, which was unknown to Doctor Spencer and to myself. The minerals had been purchased from a certain Mr. Butler, a merchant located on Broughton Road. I visited this merchant and ascertained that the case of ores had been sold to him by a Belgian officer who had spent some time on the Union Minière concession at Katanga. Upon my return to Ghent I found among these samples three other minerals which were absolutely unknown to me. I presented two of these, of an orange yellow and a dull yellow color, to the Belgian Geographical Society on April 19, 1921. All these ores were extremely radio-active."

This probably accelerated the commercial exploitation of the new radium deposits, by the Union Minière du Haut Katanga, which is one of the largest copper producers in the world. Until then the discovery in 1913 of rich radium ores in their concessions had been kept secret, due primarily to the uncertainty of the outcome of the World War and the great demand for copper during this period. But after 1920 active steps were taken to develop a radium industry in Belgium, and a large plant was built at Oolen, near Antwerp. This plant was ready for operation in August, 1922.

The ore utilized by this plant is mined in the Congo. It is packed in sacks and is conveyed overland a distance of 1600 miles to Beira, where it is loaded on cargo boats for shipment to Belgium. The radium content of this ore is about forty times greater than that of American carnotite. Furthermore, labor is cheaper in the Congo and in Belgium than in the United States. For these reasons the cost of extraction of radium is much less than formerly, and the

Union Minière has in fact a complete world monopoly. The radium industry in this country, which up to the end of 1922 produced over three-fourths of the world's total supply, was wiped out practically overnight. The price of radium came down to \$70 a milligram.

To meet the new situation, two of the radium concerns in this country, the Standard Chemical Company and the Radium Company of Colorado, made arrangements with the "Radium Belge,"—a subsidiary of the Union Minière—to sell Belgian radium in the Western Hemisphere. The extraction plants of these companies were shut down soon after. A third concern, the United States Radium Corporation, made a brave attempt to continue producing radium from carnotite ore, selling it in competition with the Belgian product. Due to the fact that practically no demand for carnotite ore existed, they were able to secure the best grade of ore at a low price, and succeeded for a time in meeting the competition. However the selling of radium in the United States on the competitive basis of the old days involved very heavy expenses and could not be carried out at the low price of \$70 per milligram. Accordingly the Radium Company of Colorado withdrew from the field in 1923. The United States Radium Corporation stopped extracting radium from carnotite in 1926, and the radium industry in this country came to an end.

EXTRACTION OF RADIUM.—For reasons which will be apparent later, radium cannot be found in nature in high concentration. In fact it is always found mixed with *at least* 2,800,000 parts of some other material. In the case of the richest pitchblende, consisting almost entirely of pure uranium oxide, the ratio is about 1 to 4,000,000. On the other hand, in good Colorado carnotite, containing 2 per cent.

uranium oxide, radium is present in the proportion of about 1 part in 200,000,000. Madame Curie would have had a much more difficult task had she attempted to isolate the radium from this ore instead of pitchblende! But once the chemical properties of radium had been determined, it became possible to extract it from carnotite—not only as a scientific curiosity, but on a commercial scale.

We need not describe here the process of extraction. It is of interest, however, to mention a few important points of the general method. Radium is very closely related chemically to barium, so that any chemical procedure which will bring about the separation of barium from the ore will be equally effective on the radium. Both barium and radium sulfates are very insoluble, hence the addition of sulfuric acid to a solution containing barium and radium will precipitate both. If the ore does not contain sufficient barium to obtain workable quantities of the precipitate, the proper amount is added.

Having effected a considerable concentration of the radium by the simple sulfate precipitation, the close chemical relation between barium and radium is no longer an advantage but is distinctly troublesome. It has not been found possible to separate the two by chemical means. Madame Curie in her pioneer work resorted to the expedient of fractional crystallization and the same method is still employed. In this, advantage is taken of the different solubility of barium and radium salts, particularly the chlorides and bromides. The barium-radium sulfates are converted to chlorides. These are more soluble in hot than in cold water. If a boiling saturated solution is allowed to cool to room temperature, about one-half of the barium and *three-quarters* of the radium present in the original solution will crystallize

out. The crystals, therefore, will contain a larger percentage of radium than the original barium-radium chlorides. By many successive repetitions of this process it is possible to obtain pure radium chloride. In practice it is found more expeditious to transform the chloride to bromide after a certain concentration has been obtained and then continue the fractional crystallizations with this salt.

The general plan of the extraction process briefly outlined here applies to all radium ores, but nevertheless the actual processes for different ores differ considerably. The quantities of ore and chemicals to be handled vary according to the richness of the ore. In the case of carnotite, to secure 500 tons of ore required to produce one gram of radium, from 2000 to 2500 tons of sandstone rock and other materials must be handled at the mines. To extract the radium from 500 tons of carnotite, an equal weight of chemicals and 10,000 tons of sulfate-free distilled water, are needed. In addition 1000 tons of coal are consumed for heat and power required in the process. These figures give an idea of the enormous quantities of materials involved in the production of one gram of radium from carnotite. The time element is also large for it takes more than six months from the mining of the ore to the finished product. The process of fractional crystallization alone extends over a period of seven to eight weeks. It must be remembered, furthermore, that in dealing with such extreme initial dilution of the desired product great care must be exercised to keep down to a minimum losses occurring at the different steps.

When pitchblende or other rich ore is used, the amount required to yield one gram of radium is much less. But since the proportion of radium in the ore is nevertheless very small—less than one part in 4,000,000—very large quanti-

ties of materials must still be handled, and the process of extraction is still formidable. Pitchblende is the richest radium ore which is apt to be found in nature because it contains as much as 80 per cent. uranium, and radium and uranium are always associated together in the ratio of 1 to 2,800,000. Accordingly radium will always be an expensive product.

RADIUM STANDARDS.—When radium was first put on the market in Europe, it was sold by the weight of the salt in which it was contained. Naturally the part of the material which was actually radium depended on the kind of salt, and particularly on its purity. Since a very small radium content was sufficient to make the material appear “strongly” radio-active, the buyer had no exact knowledge of the amount of radium he was really getting. It soon became apparent that a statement of the radio-active power of the material was highly desirable. The activity of uranium had been used by the Curies as a standard of comparison in tracing polonium and radium through the chemical analysis of pitchblende. Naturally, therefore, the same method was used to indicate the radio-active power of any salts containing radium. Thus we find in the scientific literature of the period references to 50 milligrams of radium of 100,000 activity, indicating that weight for weight the material was 100,000 times more “radio-active” than uranium.

The comparison was made by means of an instrument which measured the ionization current produced by a thin layer of the material. The ionization in the case of uranium was due to the alpha rays, whereas in the case of a substance containing radium it was due to alpha, beta, and gamma rays. The thickness of the layer, therefore, had considerable influence in the results. More important than this, however,

the irregular liberation of some radon by the radium specimen caused very large discrepancies. As soon as some fairly pure radium preparations were available, and the chief properties of the three types of radiation determined, it became evident that comparison of the different specimens by their gamma ray activity was much to be preferred. Given a specimen whose radium content is known, it is possible by this means to determine the radium content of another specimen, irrespective of the purity of the material (within certain limits).

The first problem, therefore, was to prepare a certain quantity of a pure radium salt, which could be used as a standard of comparison. Realizing the importance of having a reliable and officially recognized radium standard, the Congress of Radiology and Electricity held in Brussels in 1910 took definite steps to bring about the adoption of such a standard. The committee which was appointed for the purpose made arrangements with Mme. Curie to prepare an International Radium Standard. At this time, Hoenigschmid was engaged in the determination of the atomic weight of radium, using about one gram of pure radium chloride in the possession of the Radium Institute of Vienna. When the committee met in Paris in March, 1912, Mme. Curie's standard of 21.99 milligrams of pure radium chloride was compared very carefully by the gamma ray method with three standards prepared by Hoenigschmid and a very close agreement was found among the four. Mme. Curie's standard was accepted as the International Standard to be preserved in the Bureau International des Poids et Mesures at Sèvres, near Paris. One of Hoenigschmid's preparations was preserved as a secondary standard in Vienna. Arrangements were also made for the preparation of duplicate

standards for nations desiring them at any future time. The United States Bureau of Standards secured a secondary standard of 15.44 milligrams (radium element) in 1913.

It will be noted that the international radium standard was expressed in milligrams of anhydrous radium chloride (21.99 mg. RaCl_2). This salt is made up of 76.1 per cent. of radium (element) and 23.9 per cent. of chlorine. Accordingly the standard actually contains 16.73 mg. of radium. In comparing an unknown radium preparation to the standard, the only thing that counts is the actual radium element content of each, because this is the only part of the material which is responsible for the gamma radiation through which the comparison is made. The amount of radium in the preparation, therefore, can be expressed as so many milligrams of radium element, calculated on the basis of the radium element content of the standard. On the other hand, if the amount of anhydrous radium chloride in the standard is taken as a basis, the measurement of the unknown will be expressed in terms of this salt, whether the preparation is a chloride or any other salt. Thus one can say that a certain radium specimen contains 76.1 milligrams of radium element, or *the equivalent* of 100 milligrams of anhydrous radium chloride. The material may actually be radium sulfate of 50 per cent. purity, but since the chemical state of the radium does not influence the emission of gamma rays, this fact is irrelevant. Accordingly it is more logical to disregard altogether the chemical state of the radium and express it in terms of the radium element content, both in the case of the standard and the unknown. This is the notation generally used at the present time. It is to be regretted, however, that this notation was not generally adopted when the international radium standard was established. A great deal of

confusion resulted, particularly in medical literature, from the expression of quantities of radium in terms of the weight of various radium salts. Doses expressed in milligram hours differed considerably depending on whether "milligram" referred to radium element, radium chloride, or some other salt. If a definite statement is made of the actual notation used, there is no ambiguity, and the doses can be reduced to any other basis desired. Often, however, the term radium was used rather loosely to indicate either the radium element content of a preparation or the particular salt of which it was made up.

The practice of expressing the amount of radium in terms of one of its salts is not uncommon among European workers even now, but a statement of the salt employed is commonly made. By means of the conversion factors given below it is a simple matter then to determine the amount of radium element actually used.

1 mg. of anhydrous radium chloride (RaCl_2) contains.....	0.761 mg. radium element
1 mg. hydrated radium chloride ($\text{RaCl}_2 \cdot 2\text{H}_2\text{O}$) contains.....	0.679 mg. radium element
1 mg. anhydrous radium bromide (RaBr_2) contains.....	0.586 mg. radium element
1 mg. hydrated radium bromide ($\text{RaBr}_2 \cdot 2\text{H}_2\text{O}$) contains.....	0.536 mg. radium element
1 mg. radium sulfate (RaSO_4) contains	0.702 mg. radium element
1 mg. radium carbonate (RaCO_3) contains	0.790 mg. radium element

The first American radium put on the market in 1913 by the Standard Chemical Company was sold on the radium element basis and this notation has been used in this country almost universally ever since. At that time commercial radium was sold on the European market almost exclusively

on the basis of hydrated radium bromide, with a radium element content of 53.6 per cent. Therefore, the price of American radium appeared to be almost twice as much as that of European radium (because the chemical composition of the material was not duly emphasized). This caused some confusion in the mind of the prospective buyer who was not familiar with the subject. However the establishment in 1914 of a Radium Department at the Bureau of Standards for the measurement of radium, did much to clarify the situation.

An official measurement of a radium preparation may be obtained from the Bureau of Standards for a nominal fee. The measurement is made by comparing the gamma ray activity of the preparation with that of a radium standard. The material itself is not analyzed; in fact, it is left in the sealed container in which it is sent to the laboratory. For this reason the certificate issued by the Bureau states that "the specimen (tested) has been found to have a gamma radiation equivalent to that from — milligrams of radium element in radio-active equilibrium."

It should be noted particularly that no guarantee is given that the material measured actually contains radium. This is important because mesothorium, also a radio-active substance, emits gamma rays similar to radium rays and may be used as a substitute. From the point of view of radiation emitted, mesothorium is just as good as radium, if not better,* but its life is much shorter. A given quantity of mesothorium will disintegrate almost entirely in twenty-five years, whereas radium will lose only 1 per cent. of its value in the same period of time.

Mesothorium, being an isotope of radium, is chemically

*The gamma radiation of mesothorium products is a little more penetrating than that of Radium B and C.

inseparable from the latter. It can be distinguished readily from radium by comparing the gaseous disintegration products of the two. To do this properly, however, the material must be dissolved—an undesirable procedure when dealing with a substance of such high value. In practice it is rarely necessary to do this. The Bureau of Standards certificate states the gamma ray activity of the material and the concern selling it guarantees that this activity is due solely to radium. As a matter of fact, all ores used for the commercial extraction of radium contain such a small quantity of mesothorium that the contamination of the product by this element is entirely negligible. When mesothorium is present in appreciable proportion, therefore, it indicates a wilful adulteration.

THE CONSTITUTION OF MATTER AND THE PHENOMENON OF RADIO-ACTIVITY.—That matter consists of atoms and molecules is a very old concept formulated by Greek philosophers 400 years B.C. It was not, however, until recently that incontrovertible proof of this idea was obtained. For over two thousand years great thinkers were *speculating* about these things but they did not obtain experimental confirmation simply because they did not think of making experiments.

In modern times, the development of the atomic theory is due to the chemist. Until very recently it was considered a convenient working hypothesis which brought about a great simplification in the field of chemistry and made possible the extraordinary progress of this science during the nineteenth century. But the actual existence of atoms was not regarded as necessarily true or essential. It is to the physicist that the experimental demonstration of the existence of atoms is due, for the methods of modern physics

lend themselves better to the study of the atom than the old chemical methods.

For our present purposes it is not necessary to trace the development of the modern theory of the constitution of matter; nor is it necessary to give the experimental evidence which led to its adoption. Accordingly we shall state briefly certain well established facts which will help us materially in the study of the phenomena of radio-activity.

We all are familiar with the concept of matter as made up of atoms and molecules. Matter is found in nature in a great variety of forms, but it can be reduced to a limited number of elementary substances, known as chemical elements. An element cannot be divided by *chemical means* into simpler constituents. The smallest part of an element which retains the identity of the element is called an *atom* ("uncut"). Two or more elements may combine to form a chemical compound, in which case the different atoms arrange themselves in definite groups known as *molecules*. It is well known, also, that each element has a characteristic atomic weight. On these concepts the wonderful structure of modern chemistry has been built. But with the advent of molecular and atomic physics an entirely new vista presented itself to our senses, and this has already extended our views of the constitution of matter to a degree undreamed of as recently as the beginning of this century.

It is said that the new acquisitions in this field have revolutionized chemistry, but in reality there can be no revolution in science. A fact once *scientifically established* cannot be changed by subsequent discoveries, but its interpretation is always subject to modification. The new knowledge has brought us one step closer to the ultimate nature of things, but it has not changed chemistry. Scientific progress

is rather a process of evolution. New discoveries bring about constantly a better coördination of known facts and hence a greater simplification of the whole. There is no better illustration of this than the development of the modern theory of the constitution of matter.

A superficial examination of objects we find in nature, reveals the vast number of different substances which can be identified. A more careful study leads to the analysis of these substances into a few chemical elements. Further study brings out that all elements are made up of positive and negative electricity. Hence in the ultimate analysis the whole material universe is nothing but positive and negative electricity and we have the unification of matter and electricity. Furthermore, our present knowledge permits us to go one step forward, in that we can formulate certain definite ideas about the arrangement of the two kinds of electricity within the atom, although unanimity of opinion has not yet been reached.

The theory of atomic structure, which is generally accepted by physicists, postulates an extremely small nucleus with an excess of positive electricity, and a number of negative electrons distributed around the nucleus, sufficient to balance the positive charge of the nucleus. Thus the normal atom appears electrically neutral from the outside. Since there is a force of attraction between positive and negative electricity, it may be asked why the (positive) nucleus and the (negative) electrons do not come together and coalesce. The same question may be asked about the sun and the planets, for we know that there is a gravitational force of attraction between material bodies. In this case it is well known that the planets rotate around the sun and that the centrifugal force due to this rotation just balances the force

of attraction. Accordingly the planets travel around the sun in definite orbits. For the same reason it is assumed that the electrons of an atom rotate around the nucleus in definite orbits, thus constituting a miniature solar system.

The announcement of the atomic theory by Dalton in 1803 was followed by great activity in the careful determination of the atomic weights of chemical elements. Dalton himself assigned the value one to the atomic weight of hydrogen, and no element of smaller atomic weight has been found since. This led Prout (1815) to the idea that all heavier atoms were made up of groups of hydrogen atoms. As a necessary consequence of this hypothesis, however, the atomic weights of all elements should be whole numbers, which is not the case. At first it was supposed that more accurate determinations of the atomic weights would prove them to be whole numbers, but the most painstaking work in this field did not justify the supposition. As a result Prout's suggestion was soon discarded—but not for ever!

During the last ten or fifteen years something has happened which puts Prout's dream on a basis of reality. From a careful study of certain radio-active substances; Soddy came to the conclusion that our view of a distinct and characteristic atomic weight for each chemical element needed revision. He found some substances which have identical chemical properties (and are therefore chemically inseparable) which have, nevertheless, different atomic weights. To these substances Soddy gave the name of "isotopes." Further and more recent investigations on this subject have been carried out by Aston, with the result that a large number of isotopes have been discovered among non-radio-active elements as well. This work supplies the explanation for the existence of atomic weights which are not

whole numbers, and removes the chief stumbling block in Prout's concept of the constitution of chemical elements. For instance, potassium, which has an atomic weight of 39.1, has been found to have two isotopes with atomic weights of 39 and 41 (both being whole numbers). The ordinary atomic weight of 39.1 is accounted for by the fact that the isotope of atomic weight 41 is present only in small proportion.

More direct evidence in favor of Prout's hypothesis has been supplied by Rutherford, who has been able to tear out hydrogen atoms from nitrogen or aluminum atoms. In effect, however, the modern theory of the constitution of matter makes this a logical consequence. For, the constituents of an atom being positive and negative electricity in definite units, each atom contains sufficient "parts" with which to build a simpler atom; just as a brick house contains enough bricks with which one can build a smaller house. Hydrogen is the simplest atom, consisting only of a nucleus of unit positive charge, called a proton, and a single electron revolving about it. Accordingly it is always theoretically possible to build a hydrogen atom from the wreckage of any other atom (assuming the indestructibility and indivisibility of protons and electrons).

We shall give now a more definite idea of the internal structure of the atom according to present views. It should be remembered that it is impossible to determine this by direct observation, since the atom is altogether too small to be seen even with the aid of the most powerful microscope. It is interesting to note in passing that the limitation here is due to the fact that our sense of vision does not respond to radiation of shorter wave-length than ordinary light. If our eyes could "see" gamma rays as they see light, we could explore the atom much more easily. But as it is, all the infor-

mation must be obtained indirectly by observing the behavior of matter under certain definite conditions and then postulating some interatomic mechanism which will account for the observed facts. X-rays and radio-active radiations have supplied very effective means for the study of atomic structure.

As previously mentioned, the hydrogen atom consists of a nucleus of positive electricity (proton) and a negative electron revolving around it. The electrical charges of the nucleus and electron are equal but of opposite sign. Hence the normal hydrogen atom as a whole is electrically neutral. The extraordinary smallness of this miniature solar system may be realized from the following data:

Mass of hydrogen atom, 1.66×10^{-24} * grams.

This mass is divided between the nucleus and the electron in the ratio of 1850 to 1, and hence practically all the mass of the atom is concentrated in the nucleus. The same is true for all other atoms.

Diameter of nucleus, 10^{-16} cm.†

Diameter of electron, 2×10^{-13} cm.†

Note that although much heavier, the nucleus is smaller in size than the electron.

Diameter of orbit, 10^{-8} cm.

Orbital velocity of electron, 2200 kilometres per second. (The electron revolves in its orbit seven billion times in one-millionth of a second.)

The hydrogen atom is the simplest atom known, having one proton and one electron. Then comes the helium atom,

* The *negative* exponent (-24) here means that the decimal point in the number 1.66 is to be shifted 24 places to the left.

† Deduced from electro-magnetic theory of origin of matter.

consisting of four protons and four electrons. The four protons and two electrons are aggregated together and form the helium nucleus, while the remaining two electrons revolve about the nucleus in definite orbits. The next atom in the order of increasing complexity is the lithium atom with seven protons, four nuclear electrons, and three planetary electrons. Similar data have been obtained for all elements, uranium having the most complex atom, with 238 protons, 146 nuclear electrons, and 92 orbital electrons. It will be noted that a system with such a large number of protons and electrons must have a very intricate structure, particularly when we consider the forces which come into play. Protons repel each other and electrons do likewise, but protons and electrons attract each other. There are also gravitational and magnetic forces. All these forces of repulsion and attraction must be properly balanced, otherwise the uranium atom would not be stable enough to be identified. However, atomic structure has reached its maximum complexity in this atom. No other with a larger number of protons and electrons is known to exist in nature. In fact, the uranium atom itself is not entirely stable, and occasionally it breaks up into simpler atoms—that is, it exhibits the property of radio-activity.

We have already stated that the mass of a proton is 1850 times larger than that of an electron. Accordingly the atomic weight of an element is controlled by the number of protons in its atom. We thus have hydrogen with one proton and an atomic weight of 1, helium with 4 protons and an atomic weight of 4, and so on up to uranium with 238 for the number of protons and atomic weight.

If now we consider the electronic content of different atoms, we find that (a) the total number is equal to the

number of protons; (b) some electrons are associated with the protons in the nucleus; (c) some electrons are at a distance from the nucleus and rotate in definite orbits; (d) the number of planetary electrons varies from element to element, being 1 for the hydrogen atom and 92 for the uranium atom. There are 87 chemical elements which have been definitely identified, and five more are known to exist according to the Periodic Law, and other evidence, making a total of 92. If the elements are arranged in the order of the number of planetary electrons in their respective atoms, we have a series of 92 elements, ranging from hydrogen to uranium. This series coincides with the arrangement required by the Periodic Law, and therefore the number of planetary electrons of a normal atom determines the place which the element occupies in the Periodic Table. This is called the atomic number of the element and has a very fundamental significance.

To recapitulate, then, the number of protons in the nucleus of an atom determines the atomic weight of the element. The number of planetary electrons determines the position of the element in the Periodic Table and hence its chemical properties. It is called the atomic number. On this basis, *isotopes* (*i.e.*, elements having the same chemical properties but different atomic weights) have the same number of planetary electrons but a different number of protons. On the other hand, *isobars* (*i.e.*, elements having the same atomic weight but different chemical properties) have the same number of protons but a different number of electrons. Remembering that each atom in the normal state is electrically neutral, the number of (positive) protons and (negative) electrons must be identical. Therefore the difference between the number of planetary electrons and the

number of protons must be made up by electrons which reside in the nucleus itself. Chemical elements may differ in three ways: (1) different numbers of protons, nuclear electrons, and planetary electrons (ordinary elements); (2) different numbers of protons and nuclear electrons, but the same number of planetary electrons (isotopes); (3) different numbers of nuclear electrons and planetary electrons but the same number of protons (isobars).

From what has just been said we may infer at first thought that the removal of a planetary electron from an atom—which is a simple matter—would result in the transmutation of one element into another. This, however, is not the case because the remaining part of the atom would no longer be electrically neutral, since it would have one proton in excess of the number of electrons. The only way in which transmutation can be brought about is by altering the nucleus itself. Since this is exceedingly small, it is extremely difficult, with our present means, to carry enough kinetic energy to the nucleus to blast it to pieces.*

However, mention has already been made that the uranium atom which contains a large number of protons and electrons is not entirely stable. In fact, its nucleus breaks up of its own accord and new atoms are formed. This peculiar property which uranium and a few other elements possess is called radio-activity. It is noteworthy that all radio-active elements have atomic weights larger than 209. Evidently the large number of protons and electrons in the atomic system is responsible for the relative instability of such atoms but it is not the sole cause. The structural arrangement of the component parts has considerable influence also. For

* Rutherford has succeeded in doing this by bombarding the atom with alpha particles, because the alpha particle, being itself the nucleus of an atom (helium), is extremely small but heavy, and possesses a large amount of kinetic energy when travelling at very high speed.

this reason some elements with atomic weights lower than that of uranium are much more unstable.

This instability refers to the whole structure of the atom, but particularly to the nucleus. It manifests itself by the explosive change of one atom into another of less complexity, containing a smaller amount of potential energy. During the change, therefore, energy is liberated. A radio-active element is gradually and constantly changing of its own accord, irrespective of environmental conditions. It should be noted, however, that the *gradual change* is due to the *sudden explosion* of a certain percentage of the atoms of the element per unit time. This rate of change is different for different elements but is constant for and characteristic of each radio-active element.

RADIO-ACTIVE SERIES.—As previously mentioned, all elements with atomic weights higher than 209 (bismuth) are radio-active. The atomic numbers of these elements vary from 84 to 92 (uranium), and therefore there should be only eight radio-active elements. As a matter of fact there are many more, but the additional number is made up of isotopes which, from the ordinary chemical standpoint, do not represent separate elements. The method of analysis provided by virtue of their radio-activity, however, enables us to identify them very definitely.

Careful study of the radio-active elements has disclosed certain genealogical relations among them which have led to the classification of these elements into three series. They are: the uranium, the thorium, and the actinium series; the last named being really a “branch” of the uranium series. Since radium, with which we are chiefly concerned, is a member of the uranium series, we shall examine this somewhat in detail. It is given in Table I.

All the members of the series are true elements from the chemical standpoint. They have definite atomic weights and react as elements in forming compounds. Each element preserves its identity as long as it lasts. In order to visualize the laws governing the disintegration of radio-active substances, it is best to focus our attention on the atoms themselves. One gram of radium contains a very large number of atoms, which may be compared to the living population of

TABLE I

Element	Radiation	Half-value Period	Atomic Weight	Valence	Equilibrium Amount Mg.
Uranium 1.....	α	4,670,000,000 years	238	VI	2,830,000,000
Uranium X ₁	$\beta + \gamma$	24.6 days	234	IV	0.04
Uranium X ₂	β	1.15 minutes	234	V	0.0000013
Uranium 2.....	α	2,000,000 years	234	VI	1,180,000
Ionium.....	α	69,000 years	230	IV	41,000
Radium.....	α	1,690 years	226	II	1,000
Radon.....	α	3.85 days	222	0	0.00625
Radium A.....	α	3.0 minutes	218	VI	0.0000034
Radium B.....	$\beta + \gamma$	26.8 minutes	214	IV	0.000030
Radium C.....	$\beta + \gamma$	19.5 minutes	214	V	0.000022
Radium C'.....	α	0.000001 second	214	VI	Negligible
Radium D (Radio-lead)	Slow β	16.5 years	210	IV	9.8
Radium E.....	$\beta + \gamma$	5 days	210	V	0.0081
Radium F (Polonium).	α	126 days	210	VI	0.22
End-product (Lead)...			206	IV	(6,800,000)

the earth. Since radium is not the first member of the series, at any particular time, new radium atoms are formed from the parent ionium, while some disintegrate and are no longer radium atoms. Similarly in the population of the earth, at any given time some children are born and some individuals die. No one can predict how long a single individual is going to live, for he may die as soon as he is born or he may live one hundred years. However, from suitable mortality statistics we can determine a certain average life for the individuals of a large group. In the case of radium we must resort also to statistical methods in order to de-

termine what happens to a large aggregate of atoms. If we do this we find that the average life of an atom of radium is 2400 years.

Now let us assume that all the inhabitants of the earth suddenly became sterile. How would the population decrease from that time on? For the present discussion we may take the average life of the inhabitants to be 40 years. Then by a simple mathematical calculation we find that 2.5 per cent. of the population will die during the first year, 2.5 per cent. of the *remaining* population will die during the second year, etc. Continuing at this rate, after 28 years one-half of the population will be still living and at the end of another 28 years one-half of one-half, or one-quarter, of the original population will remain, and so on.

When radium is extracted from its ore, the amount gradually decreases since no new radium atoms are being born. From the fact that the average life of the radium atom is 2400 years we deduce that the amount will decrease at the rate of about 0.04 per cent. each year, and in 1690 years one-half of the initial amount will have disintegrated. In an additional period of 1690 years one-half of the *remaining* amount will have disintegrated and therefore one-quarter of the initial quantity will still remain. The disintegration will continue at this constant rate of one-half in 1690 years.

In the above analogy there is one important limitation which must be borne in mind. The average life of a large group of human beings is not independent of the average age of the group. That is, the *expectation of life* is not the same for individuals of different ages. Thus the expectation of life is much longer for a man of thirty than it is for a man sixty years old. Therefore, in the above example, the human

population would not decrease at the same rate each year (as we assumed) but after a certain period, would decrease at a more rapid rate and would soon become extinct. On the other hand, the expectation of life of radium atoms is the same irrespective of their age and the rate of disintegration remains constant until the number of atoms remaining is so small that statistical methods are no longer applicable. On account of the prodigious number of atoms in one gram of radium (2.75×10^{21}) the constant rate of disintegration holds even for the minutest quantities of radium we have to deal with in practice.

Just as in the case of radium the atoms of any other radio-active element have a definite average life, which may be long or very short. The reader may wonder how the average life of the atoms of a given element is ascertained, when it is impossible to trace the life history of each individual atom. The procedure, however, is very simple: Given a certain radio-active element, one can determine the *rate of disintegration* by measuring the amount present at different times. Having established the rate of disintegration, one can *calculate* the average life of the atoms of the element in question. The process is the reverse of that followed in the above discussion, where we started with a given average life and calculated the (annual) rate of disintegration. Similarly one can calculate the length of time required for half of a given amount of the radio-active material to disintegrate. This is called the "half-value period" and is related to the average life (of the atoms) of a radio-active element by the simple expression:

$$\text{Average life} = 1.43 \times (\text{half-value period})$$

Thus, for radium, the half-value period is 1690 years and the average life is $1.43 \times 1690 = 2400$ years. The mathematical

relation between the quantity Q of a radio-active element and the time t is

$$Q = Q_0 e^{-\frac{t}{a}}$$

where Q_0 = the initial amount of the element, (when $t = 0$)

$$e = 2.73$$

a = the average life of the element.

This relation holds for every radio-active element, the only difference being in the value of a , which is characteristic of each element. Usually the above expression is given in the form

$$Q = Q_0 e^{-\lambda t}$$

where $\lambda = \frac{1}{a}$ and is called the disintegration constant.

At this point it may be well to call attention to a common error in the interpretation of the half-value period. If one who is not familiar with the subject is told that one-half of any given quantity of radium will disintegrate in 1690 years, he will usually assume that the other half will also disintegrate in an additional period of 1690 years, and that, therefore, at the end of 3380 years there will be none of the initial radium left. This, of course, is incorrect, for the radium remaining at the end of 1690 years, while less in amount, is exactly the same as the initial radium, and has the same half-value period. Whence after an additional period of 1690 years one-half of one-half, or one-quarter of the initial amount, will still remain. Continuing this geometrical progression, it will be seen that a definite fraction of the initial amount of radium will still remain after one hundred thousand years. In fact, it will be about one-sixty-fourth of the initial amount.

In the case of radon, which has a half-value period of 3.85 days (see Table I), the same incorrect inference may be drawn, leading to the conclusion that no radon will remain at the end of about one week. Actually at the end of seven

days there is still 28.36 per cent. of the initial amount of radon present. A more common error, however, results from the use of the "average life" in connection with this radio-active element. The average life of *the atoms* of radon is 5.5 days, or 133 hours. The omission of the words, which are *italicized* in the above sentence, is probably responsible for the common assumption that 5.5 days, or 133 hours, is the *actual* life of a given quantity of radon. In reality, at the end of this interval there is still 37.16 per cent. of the initial amount of radon present.

The preceding discussion of the expressions "average life" and "half-value period," referring to radio-active changes, brings out their *conventional* meaning. It should be remembered that, as technical terms, each has been given a meaning which need not necessarily be apparent to those who are not familiar with the subject. In the same manner, "alveolar process" means a very definite thing to the physician, but is perplexing to the chemist, who is accustomed to an entirely different meaning of the word "process." A large part of the difficulty experienced by medical men who enter the field of radio-activity (or any other branch of physics) is due to non-familiarity with the technical terms employed by the physicist. The two expressions here considered are both apt to be misunderstood and misused. Therefore, from this point of view, there is no preference of one over the other. The "average life" has a more fundamental meaning, and also this constant enters directly in the exponential relation expressing the disintegration of radio-active matter. On the other hand, the half-value period is used more generally, and therefore is given in Table I. Either, of course, is sufficient to represent the rate of disintegration of the element.

Referring again to Table I, we find that the disintegration of radium gives rise to radon, whose half-value period is 3.85 days, as compared with 1690 years for radium. While radium is a metal, radon is a gas. Radium has a valence of II but radon is chemically inert (does not enter into chemical combination with any other element) and therefore its valence is 0. In other words, the two are as different as any two chemical elements can possibly be, and yet radium is the parent of radon.

One atom of radium, with an atomic weight of 226, expels a tiny particle of its constituent matter (alpha particle) and becomes one atom of radon, with an atomic weight of 222. The difference between these two atomic weights is four, which is exactly the atomic weight of helium. It has been found, in fact, that the alpha particle is nothing but the nucleus of the helium atom, travelling at high speed, which, as it loses its speed, gathers two electrons and becomes a helium atom. Helium is also an inert gas. Hence we have here the transmutation of an active chemical element (a metal) into two inert gases, one very heavy, and the other very light. The great difference between the original radium and the two new atoms into which it broke up, gives an idea of the violence of the atomic explosion. No wonder, then, that radio-active processes cannot be influenced by any means available at present. They take place spontaneously and cannot be either accelerated or retarded.

The energy involved in the transformation is so enormous in comparison to the space in which it is constrained that no such concentration can be approached by external means. When we shall be in a position to influence radio-active changes, we shall also be able to effect artificial transmutation of the elements and we can make gold out of lead or

mercury. This day may not be very far, for already Rutherford has been able to obtain hydrogen from nitrogen or aluminium. But here is the difficulty: he has done this only by shooting alpha particles through these elements. The alpha particle has a relatively large mass, occupies an extremely small space, and travels at the rate of 15,000 miles per second. A projectile of this sort delivers to an atom of nitrogen sufficient kinetic energy to break it up—if it hits the nucleus. Since interatomic spaces are very large in comparison to the size of atomic nuclei, direct hits are very rare.

We have said that both radon and helium are chemically inert. The latter is also non-radio-active, but radon can and does transmute itself into radium A and helium. Radium A belongs to the metal family, has an atomic weight of 218 and a valence of VI. It is not chemically inert and is very radio-active, its half-value period being only three minutes. As it changes it produces radium B and helium.

Radium B is also a radio-active metal, which, however, transmutes itself in a different way from that described so far. The atomic explosion this time gives rise to only one element, radium C (or C') and no helium. Instead of alpha particles, beta and gamma rays are emitted. The former are simply electrons travelling at very high speeds, while the latter are electro-magnetic waves similar to X-rays and ordinary light. Since only one element results from the disintegration of one atom of radium B, the atomic weights of the new element and its parent are identical, 214. Radium B has also the peculiar property of changing either into radium C or radium C', both having the same atomic weight, but still being different chemical elements. The transformation of radium B is such, however, that about 99 per cent. changes into radium C and 1 per cent into radium C'. The half-value

periods for radium B, C, and C' are different, and each is a distinct radio-active element. While they are all metals, and have the same atomic weight, 214, they are different chemical elements and occupy different places in the periodic table. Such elements are called *isobars*. Their existence was not suspected before the advent of radio-activity.

A more important modification in the concept of chemical element was also brought about by the study of radio-active substances. It was found that some elements with different atomic weights would occupy the same place in the periodic table, and were, in fact, chemically inseparable. From a chemical standpoint, therefore, they constitute one element, or, in other words, the same "element" can have more than one atomic weight or a number of components with different atomic weights. "Elements" which have identical chemical properties but different atomic weights are called *isotopes*. Their discovery marked an important step in the study of the constitution of matter.

In the uranium series (Table I) the end-product of the radio-active disintegration is an element with an atomic weight of 206, which is chemically indistinguishable from lead. Careful determinations, however, have shown that ordinary lead has an atomic weight of 207.10. How can the difference be explained? In addition to the uranium series there is the thorium series, which starts with thorium, having an atomic weight of 232 and ends with an element of atomic weight 208. There is also the actinium series, really a branch of the uranium series, whose end-product has an atomic weight of 208. Chemically all these end-products are identical with lead, and therefore they are isotopes of lead. Hence ordinary lead, with an atomic weight of 207.10, may be considered to be a mixture of these isotopes. Whether all the

lead existing at present was originally uranium or thorium, is not known. It is more probable, however, that most of the lead was formed by processes other than the radio-active process with which we are familiar. Isotopes were originally discovered among the disintegration products of uranium and thorium. More recently it has been shown that some ordinary elements, such as chlorine, are mixtures of isotopes.

A casual examination of the half-value periods of the elements in the uranium series (Table I) discloses the enormous differences existing among them. Some are very long, and some extremely short, bearing no definite relation to the respective places occupied in the series. It is, however, no mere accident that the first member has by far the longest half-value period and that it is more than four billion years. The age of the earth is probably millions of millions of years and it will readily be seen that any radio-active element with a relatively short half-value period, would have disintegrated completely during this course of time. It is on account of the very long life of uranium (and thorium) that we still have radio-active materials, otherwise we could not even tell that radio-active substances ever existed. The presence of short-lived elements subsequent to the first member is possible because they are being produced continually. In fact, they are being produced at the same rate at which they disintegrate, and consequently the amounts present remain in the same proportions. A little thought will make this clear.

Let us start with one gram of radium free of its products of disintegration. Since the half-value period of this element is very long, for the present discussion we may assume that it remains constant in amount. Then every day this quantity of radium will produce 3×10^{15} * atoms of radon, since this

* 3×10^{15} means 3 followed by 15 zeros and similarly for other exponents.

is the number of radium atoms exploding per day. (This enormous number is insignificant in comparison to the total number of atoms present in one gram of radium, 2.75×10^{21} . It represents only one-millionth of the total.) Now as soon as some radon is formed, it also starts to disintegrate at the characteristic rate indicated by the half-value period of radon (3.85 days). That is, 0.165 of the number of atoms present will explode per day. Hence at the end of the first day for every 1000 atoms of radon formed, 165 will have disintegrated, leaving a net balance of 835 radon atoms. Similarly at the end of every succeeding day there will be an excess of 835 radon atoms for every 1000 produced during the day. But the 835 atoms remaining at the end of the first day will also decrease in number during the second day at the characteristic rate of radon (16.5% in 24 hours) and therefore only 698 will remain at the end of the second day. Accordingly the total net balance at the end of the second day will be $835 + 698 = 1533$. This number is less than twice the number remaining at the end of the first day. Continuing in this manner we soon find that after a certain time (about 30 days) the amount of radon no longer increases, for the number of new radon atoms formed is equal to the number which disintegrates in the same period of time. We have then what is known as radio-active equilibrium between radium and radon. The maximum amount of radon which can accumulate from a given quantity of radium is called the equilibrium amount. The equilibrium amount of radon for one gram of radium is 0.006 milligram, and occupies a volume of 0.6 cubic millimetre at normal temperature and pressure.

By analogous reasoning we can see that there is an equilibrium amount for each member of a radio-active series. The

values for the uranium series are given in the last column of Table I, taking one gram (1000 milligrams) of radium as a starting point. Several interesting conclusions may be drawn from these figures. In the first place, since one of the descendants of uranium 1 has a half-value period of 2,000,000 years, it takes 16,000,000 years before the radio-active equilibrium for the whole series is reached. Therefore a mineral in which uranium 1 and uranium 2 are present in the proportion of 2,830 to 1.18 must be *at least* 16,000,000 years old, for once radio-active equilibrium has been reached, the amounts remain in the same proportion until the first element of the series has completely disintegrated. A mineral containing one gram of radium *must* contain *at least* 41 grams of ionium, 1,180 grams of uranium 2, traces of uranium X_1 and X_2 , and 2,830,000,000 grams of uranium 1. That is, no mineral can contain radium in greater proportion than one part in 2,830,001,221. This would be the case if "pure" uranium could be found in nature. As a matter of fact, uranium is always found in combination with other substances and so the proportion is always much less than one in three million parts of the mineral. In the case of workable carnotite it is about one part in 200,000,000, while in pitchblende it may be as high as one part in 4,000,000.

We have seen that in order to have radio-active equilibrium between uranium 1 and uranium 2 or any subsequent product, at least 16,000,000 years must elapse. This provides a means of estimating the lower limit of the age of the mineral in which, let us say, uranium and radium are in the proportions shown in Table I. Since the last product of the series, lead, is not radio-active, it will accumulate as fast as it is produced. By calculation we find that at the time radio-active equilibrium is reached in the uranium series there will

be about one part lead in 400 parts uranium. Hence assuming that all the lead in the mineral was produced by the disintegration of uranium, we can also estimate the age of the mineral. If the proportion of lead is greater than the "equilibrium amount" we can get the upper limit of the age of the mineral. Thus we can estimate very closely the age of a radio-active ore. The same reasoning can be extended to other minerals which are or have been only slightly radio-active.

The radio-active power of an element is measured by the intensity of the radiation it emits per unit mass. Considering for a moment only those elements which emit alpha particles, we may express their activity by the number of alpha particles emitted per second by one gram of the substance in question. For radium this is 3.4×10^{10} . Now in the preceding discussion of radio-active equilibrium we saw that when this condition obtains, the number of atoms changing in a given time is the same for all members of the series. This means that the same number of alpha particles is emitted, for instance by radium, radon, and radium A. Hence 3.4×10^{10} alpha particles are emitted per second by 1000 milligrams of radium, 0.0062 milligram of radon or 0.0000033 milligram of radium A. Or, weight for weight, radon is $\frac{1000}{0.0062} = 161,000$ times as active as radium, and radium A is much more active still. From this it will be seen that the radio-activity of a given element is inversely proportional to its equilibrium amount, which in turn is proportional to its half-value period. This leads to the conclusion that the more radio-active the element is, the more rapidly it changes—which is obvious.

The uranium series contains many radio-active elements, of which radium is one. Why is it then that radium has been

given so much prominence? In what does it differ from other radio-active substances? Aside from historical and sentimental reasons, due to priority of discovery and expressive name, there are more substantial reasons. In the first place its half-value period (1690 years) is so long in comparison to the span of human life that the change taking place in a lifetime is very small (1 per cent. in 25 years). At the same time its life is short in comparison to that of uranium 1 and it is about 3,000,000 times as active. But the chief merit of radium is derived by usurpation, as it were. It so happens that all the members of the series subsequent to radium have short half-value periods, and therefore reach equilibrium rapidly. Hence a short time after radium has been extracted, the equilibrium amounts of radon, radium A, B, and C will have been formed and the respective radiations from these elements are attributed to radium. Thus freshly purified radium emits only alpha rays, which are unable to pass through an ordinary glass tube container. But radium B and C soon accumulate and the original radium appears to emit beta and gamma rays. In about one month the equilibrium amounts of radon, radium A, B, and C, will have accumulated and the preparation has a maximum beta and gamma ray activity.

This activity depends on the number of radium atoms which disintegrate per unit time, for, as we have seen, the same number of atoms of the subsequent products (radon, radium A, B, and C) disintegrate in the same time. The number constitutes a small percentage of the total number of radium atoms present on account of the slow rate of disintegration, but, nevertheless, the beta and gamma radiation from a small quantity of radium is very intense. All this, of course, is only relative, for one gram of radium is a "small

quantity" because a man can lift a weight 100,000 times larger; the radiation emitted is "very intense" because we have electrical instruments which can measure the radiation emitted by less than one-millionth of a gram of radium; just as the life of radium is very long because our own is less than one hundred years. Through the combination of all these circumstances radium occupies a unique place and is considered the radio-active element *par excellence*.

From the point of view of activity, however, radium cannot hold its ground, for, as we have seen, many other elements are much more radio-active, weight for weight. Thus radon is 161,000 times more active than radium. This element, like radium, counts among its descendants radium B and C, which have the distinction of emitting the highly desired beta and gamma rays. Like radium, therefore, it can profit from the reflected glory of its offspring, and it can be used as a source of these radiations. The source, however, is not "constant" as in the case of radium, for the half-value period of radon is 3.85 days—a short time in comparison to man's life. The short life of radon is a disadvantage in some respects and an advantage in others, as we shall see later. The fact that it is a gas is also turned to advantage for many purposes. But the only way to have a continuous supply of radon is to use radium, in the same way that a cow is kept to produce milk.

In the above discussion we mentioned radium B and C as the sources of beta and gamma rays. It will be seen from Table I that radium E also emits these rays. From a practical standpoint, however, the radiations from radium E are not important, and we can say, therefore, that radium B and C are the sources of radiation we are interested in. Radium A, B, and C are solid metals, whereas radon is a gas, as

previously stated. For this reason when radium A is formed from radon, it deposits on any surface with which radon comes in contact. Radium B and C then develop on the same surface. The three constitute the "active deposit of rapid change," so denoted because the half-value periods of the three components are less than one-half hour. Radium D, E, and F, which develop subsequently and are also solid, constitute the "active deposit of slow change," radium D having a half-value period of 16.5 years.

The preparation of these active deposits is very simple, for it is only necessary to enclose an object in an atmosphere of radon for a few hours. When the object is first withdrawn it has an invisible coat of radium A, B, and C. After a few hours these three elements will have disintegrated almost completely and the deposit will consist largely of radium D. Radium E and F will then accumulate gradually as radium D disintegrates at the rate of one-half in 16.5 years. The active deposit of rapid change (radium A, B, and C) is sometimes employed for therapeutic purposes, and is usually denoted simply as active deposit.

In order to use radon for therapeutic purposes it is necessary to collect it in concentrated form so that sources of small dimensions may be available. Being a chemically inert gas, it can be separated from the parent radium by simple physical means. For instance, if a radium salt is in solution radon can be boiled out readily, or it can be extracted at ordinary room temperature by means of a vacuum pump. However, the radiations which are always present are chemically very active, and the water of the solution is partly decomposed into hydrogen and oxygen. In order to collect radon in small containers it is necessary therefore to remove these gases and water vapor which are present in large quantities

compared to the amount of radon itself. We cannot give here the details of the process of purification and collection. An automatic apparatus for this purpose is shown in Figure 1. With this it is possible to collect 500 millicuries* of radon in a capillary glass tube 20 mm. long and 0.6 mm. in external diameter. Glass tubes containing 1 mc. of radon can be made about 3 mm. in length and 0.2 mm. in outside diameter. Radon can also be collected in gold capillary tubes.

RADIUM RADIATIONS.—The radio-active change of an atom is accompanied by a readjustment of intra-atomic energy. If an alpha particle is liberated, the original atom has given rise to two new ones; if a beta particle is ejected, only one new atom results from the change. In either case, the atomic energy at the end of the change is less than that of the original atom. What has become of the balance of the energy? Since energy can neither be created nor destroyed (the Law of Conservation of Energy), it is evident that some must have escaped in some form or other. We shall now examine this question.

When the alpha particle is liberated due to an atomic explosion, it is sent flying through space at the prodigious speed of about 15,000 miles per second. The alpha particle, as already stated, is a helium atom minus two electrons, and therefore has a certain mass (four times that of the hydrogen atom). Like any other projectile, this material particle travelling at high speed has a definite amount of kinetic energy. This energy was imparted to the particle by the original atom, which, consequently, "lost" the same amount of energy. Similarly in the case where a beta particle is

* The millicurie is the unit in which the quantity of radon is usually expressed. It represents the amount of radon in equilibrium with one milligram of radium. Accordingly one millicurie of radon has the same gamma ray activity as one milligram of radium in equilibrium with its subsequent products.

ejected, kinetic energy is carried away from the atom. Since, however, the mass of the beta particle (or electron) is only $1/1850$ of the mass of the hydrogen atom, the amount of energy carried away is small in comparison to the energy of the alpha particle, in spite of the fact that the speed in this

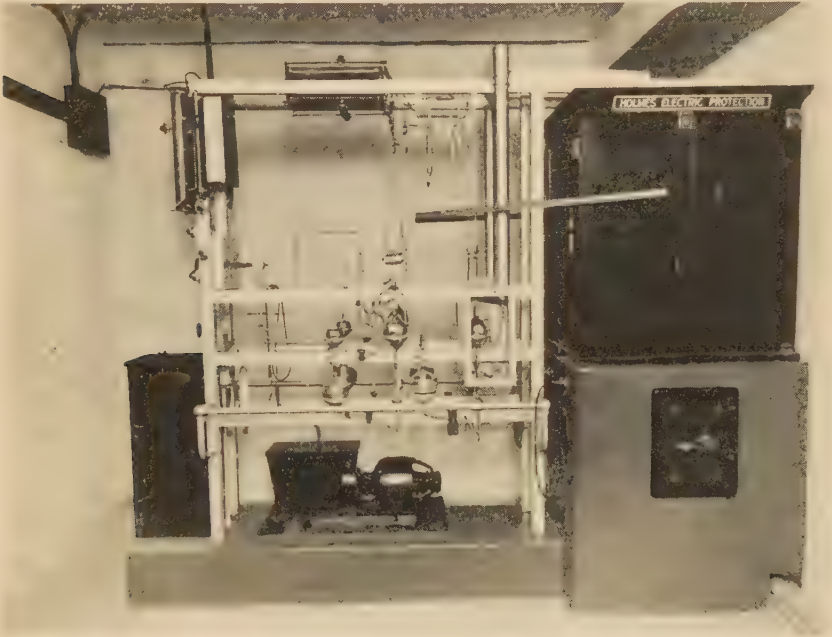


FIG. 1.—Automatic Radon Apparatus, Memorial Hospital, New York City.

case may be very close to the speed of light (186,000 miles per second).

There is a third important way in which the original atom may “lose” energy, that is, through the emission of gamma rays. This radiation is produced whenever a beta particle is liberated during the radio-active change. It seems that the expulsion of an electron from the nucleus causes intense vibration of electrons and thus electro-magnetic

energy is radiated into space. The vibrations are very rapid—about 10^{20} per second—and therefore the wave-length of the radiation is very short.*

When radio-active materials were first studied, the nature of alpha particles, beta particles, and gamma rays was unknown. Superficially they all exhibited certain properties of true radiation, and for this reason they were called alpha, beta, and gamma rays, following the precedent established by Roentgen with "X-rays." This nomenclature is still used, although it is well known that alpha and beta "rays" do not constitute true electro-magnetic radiation. The distinction should always be borne in mind because it facilitates the interpretation of the behavior of the three types.

That a radio-active substance liberates energy is evident from the fact that it is capable of affecting material bodies at a distance. Thus radium can discharge an electroscope, fog a photographic plate, or produce a skin burn, without coming in contact with the object on which it acts. But it has been possible actually to measure the amount of energy liberated. Heat being the lowest form of energy, all other forms can be converted completely into this form. Heat is also easy to measure, even in minute quantities. By surrounding a given quantity of the radio-active material with a substance which effectively blocks the escape of the radiations, the energy is confined to a small space and can be measured as heat. In the case of radium the emission of energy amounts to 134.4 calories per hour per gram of the element in equilibrium with

* The wave-length of all electro-magnetic radiation, from gamma rays to wireless telegraphy waves, is related to the frequency of oscillation as follows:

$$\begin{aligned}\text{Wave-length} \times \text{frequency} &= \text{velocity of light} \\ &= 3 \times 10^{10} \text{ cm. per second.}\end{aligned}$$

Accordingly if a radio station is operating on a wave-length of 300 metres (30,000 cm.) the electrons in the broadcasting mechanism vibrate at the rate of $\frac{3 \times 10^{10}}{30,000} = 1,000,000$ cycles a second.

its subsequent products. It has been found, furthermore, that 92 per cent. of this amount is emitted as alpha rays, 3.2 as beta rays, and 4.7 as gamma rays.* Accordingly by far the largest amount of the radio-active energy of radium is carried by the alpha particles.

In contrast to this, the alpha rays are the least penetrating, being completely absorbed by a sheet of ordinary paper, while gamma rays have the greatest penetrating power. In this connection it may be well to discuss briefly the mechanism of the passage of the radium radiation through matter.

PASSAGE OF RADIATIONS THROUGH MATTER.—According to the present theory of atomic structure, even the densest matter consists largely of “empty spaces.” That is, the protons by themselves and the electrons by themselves occupy only a fraction of the space taken up by a material object; just as the sun and planets actually occupy a small part of the space covered by the solar system. An alpha particle is extremely small but has considerable mass and is ejected with a tremendous velocity. Consequently it can “blaze a path” through matter with considerable ease. This is clearly brought out by the photographs (Fig. 2) of alpha ray paths in atmospheric air, first obtained by C. T. R. Wilson. It should be noted particularly that the paths are practically straight lines, showing that an alpha particle must actually traverse one-half million atoms which are in its direct path. These atoms, nevertheless, constitute an obstacle to the passage of the alpha particle, which in consequence is gradually retarded and finally stopped. The atoms, on the other hand, are temporarily injured, having had

*As we shall see later, the gamma rays are capable of passing through more than 15 cm. of lead, and therefore it is not practical to measure their energy by the heat method. The above figure was determined in a different way.

electrons torn off by the impact of the alpha particle, and are said to be "ionized." The initial speed of the alpha particle varies according to the radio-active substance from which it originates. But it is important to note that all the alpha particles emitted by a given element have the same initial speed. The greater this speed the farther will the particles



FIG. 2.—Photograph of alpha ray paths in air.

travel through matter. The alpha particles from radium C can be identified after traversing 6.9 cm. of air at atmospheric pressure and ordinary temperature. Their velocity is still very high—roughly 5000 miles per second—but nevertheless they cannot be detected beyond this point.* It is said, therefore, that the range in air of the alpha particles from radium C is 6.9 cm.

* By the usual scintillation or photographic methods.

The loss of energy of the alpha particle travelling through a gas is due to the number of atoms which it encounters in its path with the resultant ionization of those atoms. The same is true in liquids and solids, but since the atoms here are packed much more closely, the ranges of the alpha rays are correspondingly shorter than in gases. Thus a sheet of ordinary paper, or an aluminium foil 0.05 mm. thick is sufficient to stop the swiftest alpha particles. When radium is in a metal or even the ordinary glass container, the alpha radiation is completely stopped by the container, and therefore in this case 92 per cent. of the total radio-active energy is unavailable.

All the beta rays emitted by a given radio-active element have not the same initial velocity as in the case of alpha rays. On the contrary, their velocities vary within wide limits. However, beta rays of certain definite velocities predominate. That is, within the given range of velocities there are groups of beta rays in which the electrons (in each group) travel at the same speed. The passage of beta rays through matter is similar to the passage of alpha rays—both types of particle can “slip through” a large number of atoms. But the mass of the beta particle is only about $1/7000$ of the mass of the alpha particle, and therefore it can be deflected from a straight course much more easily by the matter which it encounters. This in spite of the fact that in general beta rays have a higher velocity than alpha rays. Figure 3 shows the path of a beta particle in air, photographed according to C. T. R. Wilson's method. The tortuous path followed by the beta ray emphasizes its great penetrating power, for, travelling in a zig-zag fashion, it can nevertheless traverse in atmospheric air, many times the distance that the swiftest alpha rays can cover.

The greater penetrating power of the beta rays is due to their higher initial velocities, which, for some particles, approach closely the velocity of light. The connection between velocity and penetrating power may be visualized by a crude analogy: Consider a large crowd running in a street and a small dog attempting to cross the street at the same time. Other things being equal, the faster the dog runs, the better the

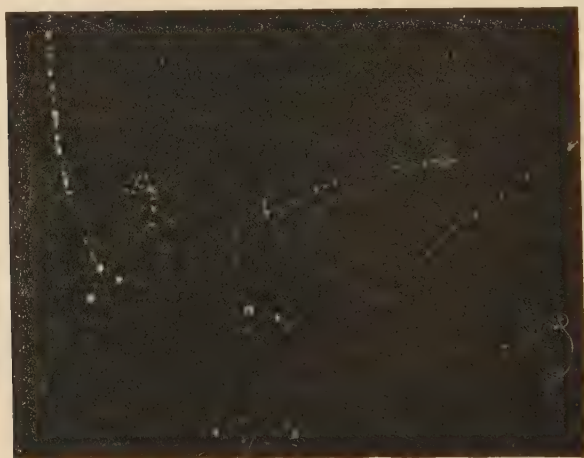


FIG. 3.—Photograph of beta ray paths in air.
(From "The Electron" by R. A. Millikan, Univ. of Chicago Press.)

chance of its crossing the street, or at any rate the farther it will penetrate into the crowd before being trampled to death. The dog will dodge the feet of the crowd and will follow a zig-zag path, perhaps even going back in the general direction from which it started. If, on the other hand, a man runs into the crowd, his large momentum, due to his heavier body, will carry him some distance through, more or less in a straight line, perhaps knocking a few men down; but progress through the crowd will soon be difficult. This is roughly analogous to the case of an alpha particle, the men in the crowd repre-

senting the atoms of matter. Naturally the thicker the crowd the shorter will be the distance through which the man will travel in his first dash, which is the case in the passage of alpha particles through liquids and solids.

From the preceding discussion it is seen that the passage of alpha and beta rays through matter may be visualized in a simple manner. When we come to the gamma rays, however, the question is much more difficult, and we shall not attempt to discuss here the mechanism of gamma ray absorption by matter, which, after all, is not definitely known. We shall bring out, however, certain points which should be borne in mind. In the case of alpha and beta rays an electric particle is shot out by the radio-active atom and travels along a certain path. In the case of gamma rays the atomic explosion gives rise to an electrical disturbance—like a flash of lightning—which is propagated simultaneously in all directions. The fact that beta and gamma rays are produced together in the change of some radio-active elements, suggests a simple analogy which emphasizes the difference between the two. The firing of a gun results in the discharge of a projectile and the emission of sound. The projectile (like the beta particle) can affect matter in its direct path and nowhere else. The sound is propagated in all directions and can affect the human ear, for instance, anywhere within a certain radius. The projectile will gradually lose speed on account of the resistance offered by the air (or anything in its path) and will finally stop. The sound will become more and more attenuated the farther it travels from the source, because it spreads over a larger and larger area (inverse square law) and because it may be absorbed by matter in its path, and finally it will be *inaudible*.

It is important to note that the distance at which the

report of a gun can be heard depends on a number of factors, some of which have a certain counterpart in the case of gamma rays. Thus the larger the gun, the greater the distance to which the report can be heard; or the larger the amount of radium the greater the distance at which the gamma radiation can be detected. The less matter (trees, walls, etc.) there is between the source and the ear, the farther the sound can be heard; or, for gamma radiation, the farther it can be detected. The *kind* of intervening matter also has an influence on the sound or radiation; felt, for



FIG. 4.—Photograph taken with gamma rays which had traversed 15 cm. of lead.

instance, is a good absorber for sound and lead for gamma rays. The kind (pitch or wave-length) of sound or gamma radiation affects the range of transmission. Thus shrill sounds do not travel very far* and gamma rays of short wave-length have great penetrating power. Aside from these factors, the sensitivity of the detector plays an important part in any practical consideration of the transmission of sound or radiation. A room may be sound-proof as far as the human ear is concerned but sound may still be detected therein by a watch dog. Surrounding a gram of radium by a certain thickness of lead may stop the visible fluorescence

* During the World War automobiles back of the fighting lines were equipped with sirens emitting a shrill sound instead of the ordinary horns.

produced in a piece of willemite, but the radiation will still be able to affect a sensitive electroscope or a photographic plate (see Fig. 4).

To recapitulate, we may say: Each alpha or beta particle is emitted in a definite direction and travels in a straight line unless interfered with. Owing to the extremely large number of particles emitted by even a minute quantity of radium and the fact that each particle may be ejected at random in any direction, the emission of alpha and beta rays *appears to be* simultaneously uniform in all directions. Absorption of alpha and beta rays by matter results from a gradual slowing down and eventual stoppage of the moving particles constituting these "rays." Absorption of gamma rays by matter results from a gradual decrease in the amplitude of the electro-magnetic waves as the radiation passes through material objects.

Since the paths of the alpha rays through matter are generally straight lines, and all alpha particles from the same radio-active substance have the same initial speed, a sheet of matter (*e.g.*, mica) of insufficient thickness for complete absorption allows practically all the particles which strike it to pass through, but their speed will be diminished. The kinetic energy of each particle will be less at emergence than it was at incidence, the difference having been absorbed by the matter. In the case of beta rays not only is the speed of each emergent particle less than it was originally, but the number of particles is also smaller. This is due to two causes: (1) The initial speed of the beta particles is not the same; (2) Each particle follows a tortuous path through the material, hence some may spend all their energy within the material and others may emerge on the incident side. On the whole, however, the loss of speed of the fastest particles is relatively small, while the slow particles are easily stopped, and conse-

quently the average velocity of the emergent beta particles is higher than that of the initial beta rays. Matter in this case "filters" out the slow speed particles, and therefore the filtered beta radiation is more penetrating. In the case of gamma rays speed has nothing to do with absorption, for all electro-magnetic waves travel at the same speed, 186,000 miles per second, as in the case of light. The controlling factor is the wave-length, the longer this is, the more easily absorbed is the radiation. Starting with a beam which contains gamma rays of different wave-lengths, filtration decreases the intensity of the long wave-length components more than it does the intensity of the short wave-length components and consequently the emergent radiation is more penetrating. It should be noted in passing that the penetration of radiation (both beta and gamma) can be increased only at the expense of the quantity. That is, after suitable filtration the radiation is more penetrating *but it is less intense*.

Any discussion of absorption of radiation is incomplete unless the questions of scattering and secondary rays are touched upon. We have already mentioned incidentally that some beta particles in following a tortuous path through matter, may actually come out in the opposite direction from which they entered. Naturally then they may come out in any direction, and the piece of matter in the path of the original rays, as it were, assumes the properties of a source of beta rays. To be sure, by far the largest number of beta particles come out in the same general direction in which the original beta rays travel, but the number of particles which deviate from this course is still large. Now it is obvious that any particles which find their way out in some way or another, are not absorbed by the matter. However, in general, they lose some velocity, and therefore some of their

energy is absorbed by the matter upon which they impinge. Furthermore, the remaining energy may be unavailable for the purposes in mind by virtue of the new paths which the particles follow. The following figure (Fig. 5) illustrates this point. R is the source of beta rays; D is a (lead) diaphragm which limits the rays to the small cone shown; Al is a sheet of aluminium in the path of the rays; S is the surface

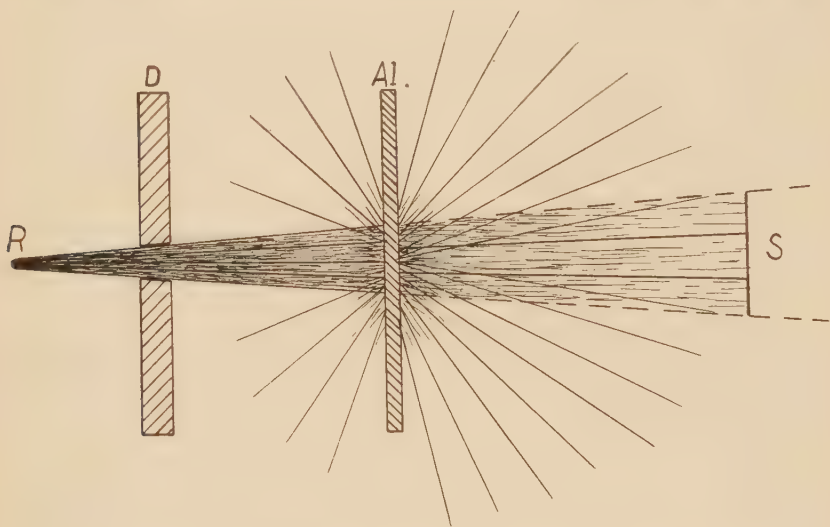


FIG. 5.—Diagrammatical illustration of the scattering of beta rays.

to be irradiated. The dotted lines show that the diaphragm is adjusted so as to give a beam which just covers the area of surface S. Some of the particles in the original beam are completely absorbed by the aluminium, and therefore cannot reach the surface S. Some are deflected ("scattered") in all directions, and of these only a few reach S. Accordingly, so far as an observer at S is concerned, the diminution in the number of particles which reach S, resulting from the interposition of the aluminium sheet, may be said to be due to the

“absorption” of the radiation by the aluminium. It should be noted that when we do this we attribute to the aluminium sheet a *greater* absorbing power than it really has. It is important to bear in mind and to think of the effect of the material screen (Al) as due to true absorption and scattering of the radiation which falls upon it.

In the case of gamma rays, the same two factors of true absorption and scattering are present, but a visualization of the mechanism is not so simple. For our purposes it is sufficient to know that they exist and that neither can be neglected. The relative part which they play in decreasing the intensity of a beam of rays depends upon the wave-length of the radiation and the nature of the material. For radiation of long wave-length, such as soft X-rays, and heavy elements, such as lead or platinum, true absorption plays the more important part. For short wave radiation such as gamma rays, and light substances, such as water, paraffin, or human tissues, scattering is more important. There are naturally gradations from these two extremes. It may be added here that in the case of gamma rays or X-rays the scattered radiation has on the average a longer wave-length than the original radiation. The scattered radiation, therefore, is on the whole less penetrating than the original radiation.

The quality of the transmitted radiation is also affected by another factor, *i.e.*, the secondary radiation produced in the matter traversed by the rays. Just as X-rays are produced by the sudden stoppage of cathode rays (high speed electrons) so will the impact of beta rays (also high speed electrons) result in the production of radiation of the X or gamma ray type. These rays are called secondary rays. The reverse process also does occur, and thus we have secondary beta rays produced whenever gamma rays traverse material

objects. These rays in turn give rise to other gamma rays, and so on. The ratio of energy transformation from one type of radiation to the other is small (just as in the case of the X-ray tube) and so the secondary radiation is not very conspicuous from the energy standpoint. However, it may assume considerable practical importance in the case of gamma rays because the secondary beta rays are easily absorbed, and on this account may produce effects out of proportion to their energy content.

We may summarize the interaction between matter and radiation as follows: A beam of (gamma) rays which traverses matter suffers a decrease in its intensity due to three causes: (1) loss of energy due to true absorption, (2) transformation of energy due to scattering, (3) transmittal of energy to secondary radiation. Matter, on the other hand, takes up energy from the radiation in two different ways: (1) by true absorption of primary, secondary, and scattered radiations, (2) in the process of scattering the primary and secondary radiations, and rescattering the scattered radiation itself.

IONIZATION.—We have just seen how energy is transmitted to matter by radium radiations. We shall now inquire how the absorbed energy manifests itself or what transformations it undergoes. At the basis of all these considerations is the fundamental fact that radium radiations exert their influence directly on the atoms of matter. The effect under proper conditions may be on the nucleus itself, resulting in the artificial transmutation of the elements. Generally, however, the planetary electrons of the atom are affected. Some electrons may be knocked out of their atomic orbits, thus being set free and finally attaching themselves to other atoms. The atom which has lost an electron has then an excess of positive

electricity, while the atom which acquires a free electron becomes negatively charged. These changed atoms are called ions ("wanderers").

The process of ionization just described is to be distinguished from chemical ionization taking place in an electrolyte. It is well known that some chemical substances, when dissolved in water, break up to a certain extent into positively and negatively charged parts or ions. A number of molecules break up in a certain definite way, forming the required number of ions to establish equilibrium. Thus hydrochloric acid (HCl) is partly dissociated into H^+ ions and Cl^- ions; calcium sulfate (CaSO_4) into Ca^{++} ions and SO_4^{--} ions. Ionization persists as long as the substance remains in solution, and no other agency is necessary. On the other hand, the ions produced by radium rays (also X-rays and ultra-violet light) are not definite parts of a molecule. One ion may consist of an atom lacking an electron, or an atom plus an electron, or a molecule plus or minus an electron, or a cluster of molecules plus or minus an electron. This type of ionization is dependent on an external agency, such as radium, and gradually disappears if the agent ceases to act. The extent to which the substance is ionized depends on the ionizing agent. But in any case, a very small fraction of the total number of atoms are in the ionized state at any one time. Since positive and negative charges attract each other, ions of opposite charges sooner or later come in contact and become electrically neutral. Thus in a substance which is under the influence of radiation, new ions are constantly formed to take the place of those which have recombined.

Ionization produced in gases can be demonstrated in a number of ways. The Wilson photographs of alpha and beta ray paths (Figs. 2 and 3) are made possible because of ioni-

zation. The photograph of Figure 6 shows the ionization produced by X-rays or gamma rays. In this connection it is of interest to note that this photograph shows streaks similar to beta ray paths (see Fig. 3). Knowing that gamma rays produce secondary beta rays, we may conclude that these paths are due to the secondary rays. Furthermore, in the absence of a uniform and continuous distribution of ions in the photograph, we may conclude that most, if not all, of the ionization produced by gamma rays is due to the secondary beta rays. This would indicate that the action of gamma radiation



FIG. 6.—Photograph showing ionization of air produced by gamma rays.

on matter is an indirect one and takes place through the intermediary of secondary beta rays. Ionization in liquids may be demonstrated by the electrical method of which we shall speak presently. Ionization in solids is difficult to study, but undoubtedly it exists, as indicated by chemical changes which are brought about by radiation.

Ionization has been studied chiefly by the electrical method and in turn this has supplied the best method of studying the ionizing rays themselves. We shall, therefore, take up this question somewhat in detail. Knowing that water is made up of molecules, we can think of a current of water as the migration of these molecules, from one point to another. In an analogous way an electric current is nothing but a number

of electric charges moving from one point to another. The carriers may be the electrons themselves, or ions of any kind, or even dust particles. The essential thing is that electric charges be in motion. Just as a force must be applied to set water in motion (usually the force of gravitation), a force must be applied to the electric charges to produce a current. Such a "force" is called an electromotive force (e.m.f.) and is ordinarily expressed in volts. The terms "potential" and "voltage" are also used to express the same thing.

If we have two parallel metal plates insulated from each other by an air space, and apply a certain e.m.f. to them, no appreciable current flows from one plate to the other, even though the applied voltage be quite high. The reason is that ordinary air contains no free electrons and only very few ions. Allowing a beam of radium rays to pass through the air results in the formation of ions, and a current is established. The negative ions travel towards the positive plate and the positive ions towards the negative plate. The magnitude of the current depends on the number of ions reaching the plates per second. This in turn depends on the radiation which is ionizing the air and on other factors which we shall mention later. From what has just been said it may be surmised that by measuring the electric current produced by ionization we can get a measure of the radiation responsible for it.

We have already mentioned the recombination of ions in an ionized medium. This has an important bearing on ionization measurements. Recombination takes place at all times, and the number of ions present at any instant is the difference between those that have previously been formed and those that have already recombined, or have otherwise been neutralized. Since the rate of recombination naturally

affects the magnitude of the ionizing current, it must be controlled in some way when quantitative measurements are required. The best way to do this is to prevent it—which can be done in a simple manner. It takes a certain time, however short, for ions of opposite charge to come together. If, therefore, we can make them reach the metal plates in a shorter time than this, they will have little chance for recombination. This can be done by applying a sufficiently high voltage to the plates. We then obtain the maximum current which the degree of ionization permits. It is called the *saturation current* and can be taken as a measure of the number of ions produced per second in the air between the charged plates by the radiation. It is, perhaps, hardly necessary to add that the farther apart the plates are, the higher the voltage must be to obtain the saturation current. Also the more intense the ionization is, the higher the voltage must be, since recombination can take place more easily.

From the preceding discussion it is apparent that to establish an ionization current, in addition to the presence of ions, it is necessary that they should travel to the charged plates. Furthermore, in order to obtain saturation current, it is necessary that they reach the plates before they have had an opportunity to recombine. The mobility of the ions, therefore, is an important factor in this connection. In gases they can move freely. But, remembering that ions are always of molecular dimensions, we can easily see that their motion must be considerably impeded in liquids and solids. Accordingly, in spite of the closer packing of the molecules, ionization currents of this type in liquids and solids are in general much smaller than in gases. In addition it is difficult to obtain saturation current. In practice, air or some other gas is ordinarily used as the ionizable medium.

Reference has already been made to the minuteness of the ionization currents under discussion. On this account very delicate electrical instruments must be used and great care must be exercised to avoid effects on the instrument due to extraneous causes. There are very sensitive galvanometers of the D'Arsonval type which can measure a current of one-billionth of an ampere (or even less) but for ordinary radioactive measurements even these instruments are too insensitive. Furthermore they require very careful handling. The instrument which is generally employed is the gold leaf electroscope. If properly designed, this instrument can have a very high sensitivity and at the same time it can be quite rugged. However, an electroscope (or electrometer) does not give a direct measure of an ionization current, and therefore an additional measurement (of time) is required to determine the current.

The essential parts of an electroscope are shown in Figure 7. A strip of gold leaf *G* about 2 mm. wide and 25 mm. long, is attached at one end to a flat brass post *P* which is supported on a good insulator *I*. The metal case *C*, which houses the leaf, may be of any desired size and thickness. The leaf system is charged to a potential of 300 volts (or whatever is necessary to produce saturation current) by making contact with a suitable source of potential through the rod *R*. On account of the force of repulsion between the electricity in the gold leaf and that in the post, the leaf assumes a position such as at *a*. The higher the charging potential, the farther will the leaf stand out from the post. Each position then corresponds to a definite voltage and in turn to a definite quantity of electricity contained by the leaf system. When the rod *R* is withdrawn, the electroscope is left charged and the leaf remains away from the post, since the latter is sup-

ported by a good insulator *I*. If now ions are produced in the air within the electroscopes case, those carrying charges of opposite sign to the leaf charge will be attracted to the leaf system. When they come in contact with it they neutralize some of the electricity in the system and therefore the leaf moves to a lower position, such as *b*. The downward motion

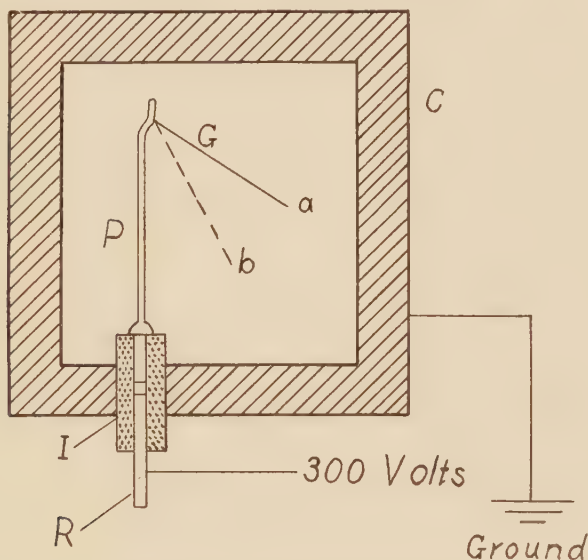


FIG. 7.—Simple model of gold leaf electroscope.
(From "The Electron" by A. A. Millikan, Univ. of Chicago Press.)

will continue until the leaf is completely discharged. It is evident that the more ions are formed within the electroscopes, the faster will the leaf drop to a vertical position. Therefore the time required for the leaf to travel from, let us say, position *a* to position *b* is dependent on the degree of ionization and in fact is inversely proportional to the ionization current. Accordingly the time required for a given travel is inversely proportional to the intensity of the radiation which is responsible for the ionization. In practice the

time interval is measured with a stopwatch and the motion of the leaf is observed either by means of a telescope or by projecting its image on a ground glass screen.

Radium preparations are sold on the basis of the amount of radium element they contain. This is determined by means of an electroscope or other similar instrument. The process is as follows: Taking a tube of known radium content (the standard), we place it at a suitable distance from the electroscope, behind a lead plate two or more centimetres thick. Gamma rays emitted by the radium, after traversing the lead plate, will ionize the air in the electroscope and the gold leaf will move downward. Let us say that the tube contains 50 milligrams of radium and that it takes 30 seconds for the leaf to travel between the points *a* and *b*. The radium preparation, whose radium content we wish to determine, is then placed in exactly the same position with respect to the electroscope in which the 50-milligram tube was. The time of discharge from *a* to *b* is now found to be, let us say, 60 seconds. Then the amount of radium element in the unknown preparation is $\frac{30}{60} \times 50 = 25$ milligrams. As

already mentioned it is important to place the standard radium tube and the unknown preparation in exactly the same position. If they are at different distances from the electroscope the comparison is incorrect. Also if the two are very different in size and shape an appreciable error may be introduced. The reason for using a thick lead plate to filter the rays is primarily to minimize errors due to differences in the absorption of the containers and the salt itself. Gamma rays, being very penetrating, are little affected by small differences in filtration. Nevertheless, for accurate measurements, allowance must be made for such differences.

Use can be made of the ionizing power of radium rays to study the radiations. For this purpose it is generally preferable to employ a modified electroscope to meet the special requirements of the problem in view. For instance, if the relative ionizing powers of beta and gamma rays depending on the filtration are to be determined, the radiation should traverse very little filtering material before reaching the air in which the ionization is measured. A separate ionization chamber electrically connected to the electroscope is desirable in this case. Again if the space distribution of the radiation in an absorbing medium such as water is to be investigated, a very small ionization chamber is required. The design of the necessary apparatus for the solution of particular problems involves many considerations which naturally we cannot discuss here. We might say, however, that the influence of the method and apparatus used on the results obtained may be very important and must always be borne in mind.

Ionization is only one of the many effects which may be produced by radium radiations. Information obtained from the study of the radiations by ionization methods, therefore, *may not* apply directly to other effects. A simple example will illustrate this point. Let us take three definite beams of light, red, blue, and ultra-violet, of given wave-lengths. We wish to measure the "quantity" of light in each beam by (1) visual comparison, and (2) the darkening of a photographic plate. Employing the first method (visual) we find that the red and blue beams have, let us say, the same apparent intensity; while the ultra-violet beam, being invisible, will seem to have zero intensity. On the other hand, using the ordinary photographic plate as an indicator, we find that, for equal exposures, the red light produces practically no

blackening while ultra-violet light has a very marked effect. On this basis we would conclude that the beam of red light has a very low intensity and the ultra-violet beam the highest one. The true intensity of radiation, however, may be the same for all three beams. The results will depend also on certain properties of the "apparatus." Thus in the visual comparison a color blind person will get an entirely different result from that of a normal individual. In the photographic tests also a good deal depends on the kind of plate used.

Radium radiations exert their influence on the atoms of matter. Ionization is the immediate manifestation of this effect. Atoms which have been ionized are in a more favorable condition to react chemically. As a natural consequence, therefore, the radiations produce chemical changes. Organic substances, with their complex molecules, are more apt to be affected by the rays. Living tissues, which depend on a more or less critical interlocking of chemical reactions, are therefore still more apt to be affected by radiation. The foregoing statements offer an explanation for the observed facts about the action of radium rays on matter. To produce perceptible changes in inorganic substances, very large amounts of radiation must be used. Organic substances can be affected more easily, but large amounts of radiation are still required. On the other hand, biological changes can be brought about by relatively small doses of radiation.

In the light of these considerations ionization assumes a most important rôle in the action of radiation on matter. Accordingly one might expect a close relation between ionization and other radiation effects. However, ionization may be produced by radiation differing widely in type and quality and with our present limited knowledge it is at least risky to assume that any particular effect depends simply on

the ionization produced irrespective of the type or quality of the radiation which is responsible for it. For this reason we have emphasized before the influence which the method and apparatus may have on the results of any investigation of the properties of radiation.

PRACTICAL CONSIDERATIONS

DOSAGE.—Rational therapy depends on the proper correlation of *dose* and *effect* for any agent which may be employed. This requires, in the first place, an accurate knowledge of the *dose*. In drug therapy it is necessary to specify the *kind* of drug used, the *amount*, and the *mode of administration*. Similarly in radiation therapy the same three factors must be specified, but the problem is more complicated. In specifying the kind of radiation it is not sufficient to say “radium” or “X-rays” or “light,” for the radiations in each of these groups are very complex. In the case of radium with which we are chiefly concerned here, there are three very different types of rays, and there are differences within each type. Practical requirements, however, are fully met by specifying the *filtration*.

The specification of the amount used is the most difficult part of the problem of dosage in radium therapy. Radium may be applied on the surface of the lesion, at a distance, or within the tumor mass, and in various other ways. During the treatment the radium has *emitted* a definite amount of radiant energy. Can we say that this represents the amount of radiation used? Obviously the radiation which does not reach the tissues to be treated cannot be of any use. Therefore it is not the emitted radiation which is important as a dosage factor, but the radiation which acts upon the tissues (normal as well as pathological). This depends upon the

mode of application of the radium, which embodies the following factors: (1) the quantity of radium, (2) the duration of the irradiation, (3) the filtration, (4) the distribution of the source, (5) the distance or spacing, (6) the geometrical configuration of the tissues, (7) the absorbing power of a tissue for the particular radiation which reaches different points therein. It is evident therefore that stating only the amount of radium used in a given treatment is utterly inadequate. Nor is it sufficient to say that a certain number of "milligram hours" were used, because this includes (implicitly) only two of the factors enumerated above—the quantity of radium and the duration of the irradiation. Accordingly milligram hours (or millicurie hours) express the amount of radiation liberated by the radio-active source, but not at all the amount of radiation administered to the tissues.

The third factor (previously mentioned) which is needed to define a radiation treatment is the *mode of administration*. By this we mean particularly the time spacing of the irradiations. The same total amount of radiation may be administered at one time or by several fractional treatments. In either case each treatment may be long or short depending on the amount of radium used. In general the biological effect produced will depend on the particular scheme chosen, and therefore it is important to specify the mode of administration. In practice this can be done with little difficulty but care must be exercised not to omit details which, while apparently trivial, may really be essential.

In the following paragraphs we shall attempt to show the importance of the different factors mentioned above. We shall do this by giving some quantitative data which bring out the relative effect on the radiation delivered to the tissues due to certain typical changes in the different treatment

factors. The information supplied will be sufficient to serve as a definite guide to the radium therapist in arranging the mode of application of the radio-active agent to meet particular requirements. In order to estimate the actual amount of radiation delivered to different points in the irradiated tissue under all conditions of treatment, much more information is needed. Some will be found in the publications we list at the end of this chapter, and some is not available at present.

QUALITY OF RADIATION, AND FILTRATION.—Filtration determines the *kind* or *quality* of the radium radiations employed. Just what effect different filters have can be determined by ionization measurements as previously outlined. Without describing here the exact experimental conditions* we shall give the results of such measurements.¹ Starting with a small glass tube containing radon, a measurement is taken of the radiation which it emits. Then one millimetre of pure gum rubber is interposed between the radon tube and the ionization chamber and a measurement is made of the radiation which now ionizes the air in the chamber. The difference gives the amount absorbed by one millimetre of pure gum rubber. (This material was chosen because it is organic and its absorption differs little from that of the average human tissue.) The same procedure may be repeated with additional thicknesses of rubber, or the addition of metallic filters and then rubber. Taking as a criterion of the quality of radiation the amount absorbed in one millimetre of rubber, we give in the second column of Table II the relative measure of the quality of radium rays filtered by various thicknesses of brass. Examining the transmitted radiation as to beta and gamma ray compo-

* These may be found in the publications referred to.

nents we get the relative values of the last two columns of Table II.

It will be seen that filtration by brass from 0 to 2 mm. in thickness: (1) increases the penetrating power of the radiation and (2) decreases the relative proportion of the beta radiation in the transmitted beam. These two effects are not independent, for the rapid increase in penetration with the addition of thin brass filters is related to the marked absorption of beta rays by the filter. The figures of Table II indicate clearly how the quality of the radiation can be defined by the filter. To each thickness there corresponds a definite quality as indicated by the degree of absorption suffered by the radiation in going through one millimetre of rubber.

As just pointed out, filtration changes the quality of the radiation. It does this by virtue of the unequal absorption of beta rays of different speeds or gamma rays of different wave-lengths. It is therefore a process of uneven subtraction of radiation from the primary beam. Accordingly the intensity* of the radiation in the transmitted beam is also affected.

The figures of Table III indicate the relative intensities of the transmitted radiations for different brass filters. Coincident with the rapid increase in the penetrating power of the radiation (Table II) there is a rapid decrease in its intensity (Table III). For a filter of 2 mm. of brass, which is sufficient to remove all the beta radiation, the transmitted radiation is only 2.8 * per cent. of the amount transmitted by

*The "intensity of radiation" at a given point is defined as the amount of energy passing per second through an area of one square centimetre placed at the point in question perpendicular to the line of propagation. To determine this quantity it is necessary to measure the total energy passing through or a known fraction thereof. However, when the radiation is complex, ionization measurements do not fulfil this requirement and therefore the values obtained by this means do not represent the true intensity of radiation. These values involve the effectiveness of different radiation components in producing ionization. The term is used here with this proviso.

the radon tube. High penetrating power is therefore obtained at a great loss of available radiation.

The absorbing power of a metal depends on its density

TABLE II
Modification of Quality of Radium Radiations by Filtration

Filter mm. Brass.	Per Cent. Absorbed in First mm. Rubber	Composition of Radiation	
		Per Cent. Beta	Per Cent. Gamma
0	73	96.5	3.5
0.1	36	91	9
0.2	23	65	35
0.4	12	46	54
0.7	5.4	18	82
1.0	3.5	4.5	95.5
1.5	2.3	1.4	98.6
2.0	1.3	0	100

and atomic number. The higher both are, the more radiation the metal will absorb per unit thickness. But in any case by proper choice of thickness a gradation in the quality of

TABLE III
Influence of Filtration on the Quantity of Radiation Transmitted

Filter mm. Brass	Percentage of Total Radiation Transmitted	Percentage of Each Type of Radiation Transmitted	
		Beta	Gamma
0	100	96.5	3.5
0.1	35.2	32	3.24
0.2	10.8	7.6	3.15
0.4	5.8	2.7	3.07
0.7	3.7	0.67	3.01
1.0	3.1	0.14	2.96
1.5	2.9	0.04	2.89
2.0	2.8	0	2.82

radiation can be obtained as in the case of brass (Table II). The thickness of two widely different filters (brass and platinum, for instance) can be adjusted so that the total amount

of radiation transmitted is the same. But on account of differences in the relative scattering, absorption, and secondary ray production of the two materials, the *quality* of the transmitted radiation in general may be quite different. The two filters, therefore, while equivalent in one sense, are not really equivalent. This is particularly true for thin filters, which allow a substantial proportion of the beta radiation to pass through.^{1, 2} Brass, silver, lead, gold, and platinum are often used as filters in *gamma ray* therapy. In this case "equivalent" thicknesses of these materials give essentially the same quality of gamma radiation, particularly when an additional filter of low atomic weight is used to remove the secondary beta rays.

Due to a number of factors, which we cannot discuss fully here, "equivalent" thicknesses of different filtering materials depend to some extent on the radiation effect³ which is used to determine the equivalence. Taking skin erythema^{4, 5} as the standard of comparison, equivalent thicknesses of most common filters can be determined from the curves of Figure 8.¹ The ordinates represent percentages of the transmitted radiation effective in producing skin erythema, and the abscissæ the filter thickness in millimetres. As an example we may determine the thickness of silver, lead, and platinum equivalent to 0.5 mm. of brass.* From the 0.5 mm. point of the horizontal axis draw a line AB intersecting the curve for brass at B, then draw the horizontal line BC. The thickness corresponding to the intersections S, L, and P of this line with the respective curves for silver, lead, and platinum, are the ones desired. They are: silver, 0.32 mm., lead, 0.29 mm., platinum, 0.13 mm. To

* This particular example was selected because it brings out best the method of determining equivalent thicknesses by means of Figure 8. For thicker filters the curves should be plotted to a larger scale.

each must be added a secondary filter of 1.0 mm. of pure gum rubber, since such a secondary filter was included in the data for the curves of Figure 8. (The secondary filters used for different metal thicknesses are also given in Figure 8.)

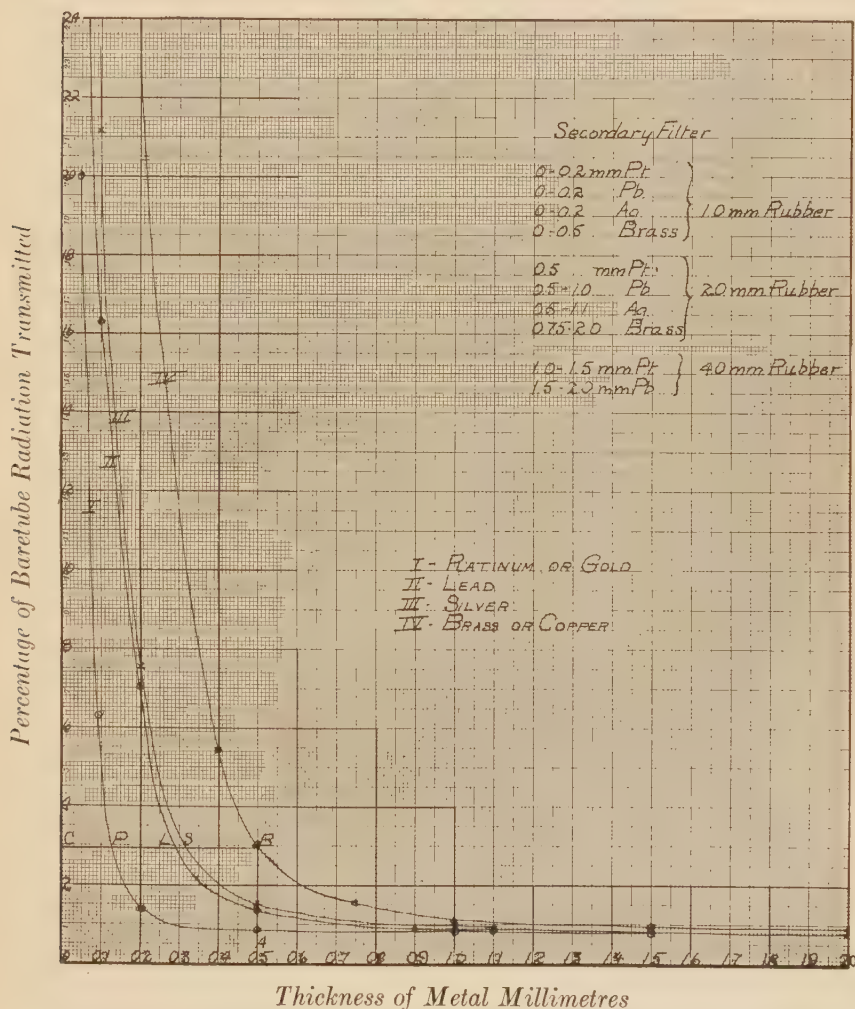


FIG. 8.—Absorbing power of different metallic filters.

The "equivalence" here means that, other conditions being equal, the same milligram-hour dose will produce the same skin erythema with each of the above filters.

By filtration is meant the intentional total or partial absorption by a suitable material of some components of the radiations emitted by radium in order that the remaining radiation may be best adapted for the purpose in view. This is ordinarily done by enclosing the radio-active material in a suitable metal container which acts as the filter. Only the radiation which comes out of the container is of interest, and this in general is a small fraction of the total amount of energy emitted by the radium. (Ninety-two per cent. is in the form of alpha rays.) This loss is of no particular significance except from the economic point of view. We must pay the price if we wish to use highly penetrating radiation.

ABSORPTION AND SCATTERING OF RADIATION BY TISSUES.—There is one loss due to absorption which not only decreases the available radiation, but imposes a serious limitation upon radium therapy. We refer now to the absorption of radiation by normal tissues. Since radium rays exert their influence upon the atoms of matter themselves, the grouping of the atoms which determines the structure of a substance has nothing to do with the absorption. One cubic centimetre of tissue absorbs the same amount of radiation whether it is living or dead, structurally intact, or ground to a pulp, provided there is no change in mass and the same chemical elements remain in the original proportions. It follows, therefore, that tissues having the same density and the same chemical composition absorb radiation to the same extent. Normal and pathological tissues do not differ greatly in either regard, and so there is no marked difference in their absorbing power. Accordingly when a deep-seated tumor is treated

by the external application of radium all the tissues absorb radiation approximately in proportion to the amount of radiation which reaches them. Therefore, the superficial tissues, which intervene between the source of radiation and the tumor, actually absorb more radiation (per unit volume) than the tumor, because more radiation reaches them. Whether the tumor can be influenced favorably by the amount of radiation which the intervening tissues allow to pass, will depend, among other things, on the relative susceptibility of the pathological and normal tissues. For, the amount of radiation which can be administered to the normal tissues is limited by the danger of injury to these tissues, and the amount which reaches the tumor is always a fraction of this amount. Accordingly, while the absorption of the radiation by the filter simply decreases the "strength" of the source, absorption by the tissues decreases the *relative* amount available at the tumor, and the *absolute* amount depending on the tolerance of the normal tissues. The absorption of radiation by tissue, therefore, appears as a serious impediment. Nevertheless it is essential because no tissue changes could be produced if there were no absorption.

The absorption of radiation by a tissue depends on the quality of the radiation and on the tissue itself. The curves of Figure 9¹ show how radiation filtered by different thicknesses of brass is absorbed by pure gum rubber (which may be used as a tissue substitute in this case). The larger the filter thickness the smaller is the absorption per centimetre of rubber, as shown by the smaller drop in the curves for the thicker filters. For the external treatment of deep seated tumors, therefore, heavy filtration should be used in order to minimize as much as possible the absorption in the intervening layers of normal tissues. Remembering, however, that

filtration decreases the amount of radiation available we are led to inquire how far it is practically desirable to

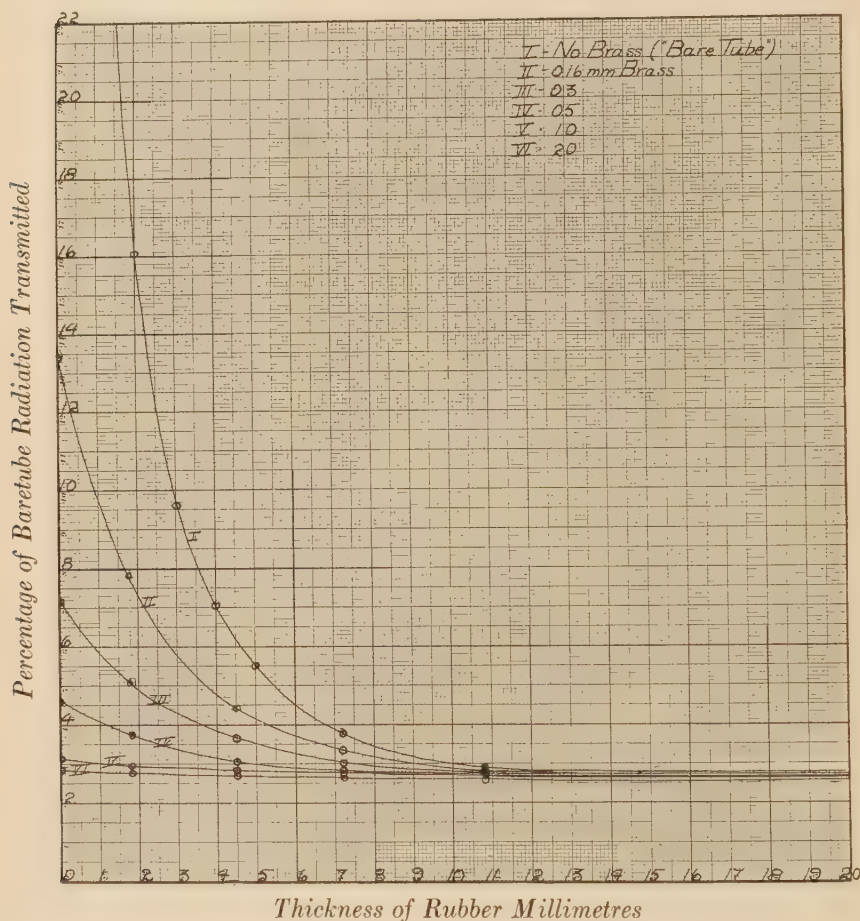


FIG. 9.—Absorbing power of pure gum rubber for radium radiations of different quality.

increase the filtration of radium rays. A filter of 2 mm. of brass is sufficient to remove all, or practically all, of the beta rays and the less penetrating components of the gamma radiation.¹ The make-up of the gamma radiation thus

filtered is such that considerable additional filtration is required to increase appreciably the penetrating power of the radiation. This is particularly true when tissue penetration is considered, because in this case scattering, and not true absorption is the predominant effect. The additional filtration, therefore, will decrease the gamma ray intensity out of proportion to the small increase in penetration. Accordingly 2 mm. of brass (and a few mm. of rubber or other secondary filter) is a sufficient filter for gamma ray therapy.⁶ Some radiologists, however, prefer to use heavier filtration—2 or

TABLE IV
Absorption of Gamma Rays by Different Animal Tissues

Organ	Density	Per Cent. Absorbed per Cm.
Solid bone.....	2.01	13.0
Porous bone.....	1.15	7.5
Liver.....	1.06	7.4
Spleen.....	1.05	7.3
Muscle.....	1.03	6.9
Brain.....	1.03	6.6
Suet.....	0.94	6.5
Lung.....	0.78	4.5

3 mm. of lead, or 1 or 2 mm. of platinum—on the basis that the radiation thus filtered exerts a more “selective action” on cancer tissues. This point can hardly be said to be well established, and it is doubtful whether the difference in “selectivity” in this case would be appreciable if it did exist.

The relative absorbing power of different animal tissues (beef) may be seen from Table IV.⁶ With the exception of solid bone and lung there is not much difference in the absorption of gamma rays by one centimetre of each tissue. The variation is in accordance with the variation in density, as might be expected.

The scattering of radiation by tissues influences also the amount which reaches a given depth. Let us consider one cubic centimetre of tissue at a depth of 5 cm. within a large mass (Fig. 10). Scattering by the tissue directly in the path of the rays (the shaded portion of the figure) tends to decrease the amount of radiation reaching the small volume V. Scattering by the remainder of the tissue mass tends to increase the radiation at V as shown roughly in the figure.

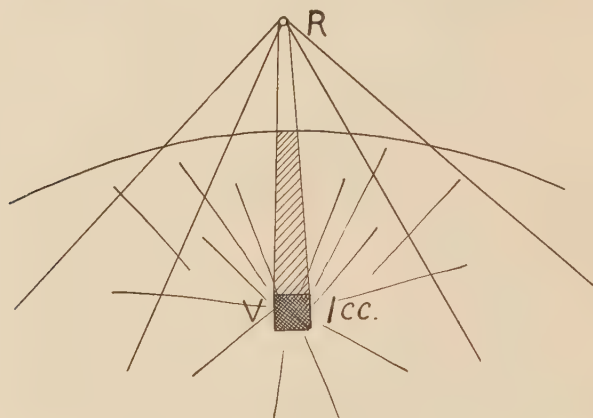


FIG. 10.—Diagrammatic illustration of the effect of scattering on the radiation which reaches a given tissue depth.

When large radium packs are applied over the region of the chest or abdomen a large volume of tissue is irradiated and scattering is responsible for a considerable proportion of the radiation reaching the deeper layers. The contribution by scattering to the amount of radiation effective at a depth increases with the depth and may become larger than the amount of radiation arriving there by direct transmission of the original beam.⁷ Furthermore, since the scattered radiation is less penetrating than the initial radiation, it is biologically more effective. This indicates how important the effect of scattering may be under certain conditions, that

is, when a deep-seated tumor is irradiated by large radium "packs." However, when radium is used locally or interstitially the intense effect produced in the immediate neighborhood of the radium is chiefly due to the direct radiation.

DISTANCE.—Aside from any effect of matter on the rays of radium, the intensity of the radiation decreases as the distance from the source increases. This is purely a geometrical consequence of the emission of radiation in all directions. For a point source there is a simple mathematical relation between intensity of radiation and distance, which can be derived in the following way: Assume that the (point) source emits Q units of energy per second. This energy is emitted uniformly in all directions. If the source is at the centre of a sphere of radius D , all the emitted energy passes through the area of this sphere, which is $4\pi D^2$. Therefore the amount passing through per square centimetre per second is $\frac{Q}{4\pi D^2}$ units. Since by definition this is the *intensity of radiation* I , we have $I = \frac{Q}{4\pi D^2} = \frac{Q}{4\pi} \times \frac{1}{D^2}$. The factor $\frac{Q}{4\pi}$ is independent of the distance and therefore I is directly proportional to $\frac{1}{D^2}$ or *inversely* proportional to the square of the distance. This relation is usually called the *Inverse Square Law*.

It will be seen then that even when there is no absorbing material to effect the radiation, its intensity decreases rapidly with the distance from the source. Calling the intensity at a distance of one centimetre 100 units, the relative intensities at longer distances are given in the second column of Table V. The rapid decrease is seen at a glance. In the third column are given the actual differences in intensity

between successive centimetres. Thus the radiation reaching the second centimetre distance from the source is 75 units less than the radiation at the end of the first centimetre. The radiation at 5 cm. is 2.25 units less than the radiation at 4 cm. This shows that as the distance increases the difference of intensity between successive centimetres becomes smaller and smaller. The rapid drop indicated by the figures (of the third column), however, is more apparent than real, because less radiation is present at greater distances. The percentage differences, which are more significant, are given in the last

TABLE V
Effect of Inverse Square Law

Distance	Intensity	Difference Between Successive Cm.	
Cm.	Per Cent.	Actual	Per Cent.
1	100		
2	25	75	75
3	11.1	13.9	56
4	6.25	4.85	44
5	4	2.25	36

column. Thus while the radiation at 2 cm. is 75 per cent. less than the radiation at 1 cm. the radiation at 5 cm. is only 36 per cent. less than that at 4 cm. This has an important bearing on the treatment of deep-seated tumors by external applications.

Let us consider, for instance, a tumor at a depth of 10 cm. below the surface of the skin. If we place a (small) tube of radium at a distance of 5 cm. from the skin and call the radiation falling on the skin 100 per cent., then due to the additional 10 cm. distance, the radiation intensity will have been decreased to $\frac{5^2}{15^2} \times 100 = 11.1$ per cent. at the tumor level, without considering tissue absorption. If, on the other

hand, the radium is placed at a distance of 10 cm. from the skin, the amount reaching the tumor would be $\frac{10^2}{20^2} \times 100 = 25$ per cent. of the amount falling on the skin (neglecting again tissue absorption). Therefore by increasing the distance of application we can increase the *relative* amount of radiation delivered to the tumor. To obtain a corresponding increase in the absolute amount of radiation at the tumor it is necessary to deliver to the skin the same radiation as in the previous case. Making use again of the inverse square law we find that for the 10 cm. distance four times as much radium is required to give the same intensity at the skin as for the 5 cm. distance. Therefore, to increase the radiation at a depth of 10 cm. from 11.1 per cent. to 25 per cent. it is necessary to use four times as much radium (or for the same amount of radium the duration of the treatment must be four times as long). In these examples we have considered only the effect of distance. In any actual case, however, tissue absorption and scattering must also be considered. Since these two effects tend to compensate when only gamma rays are used, the values given above are really not very much in error. Accordingly the operation of the inverse square law is chiefly responsible for the rapid decrease in the intensity of radiation with increasing tissue depth.

DISTRIBUTION OF RADIO-ACTIVE SOURCE AND RADIATION.

—The inverse square law is applicable only to a *point* source, but there are no true point sources of radiation in practice. However, when the radium container is small and the distances considered are *relatively* large, the error introduced by the use of this relation is negligible. For large containers and short distances the inverse square law is not applicable to the source taken as a whole, but is applicable to each point

of the source considered by itself. Making use of this fact, and making proper allowances for filtration according to the biological effectiveness of the radiation, tables have been worked out⁸ which give the relative intensities of radiation at different distances from applicators of various shapes and sizes. The data for gamma ray applicators are given in Table VI. The filter in every case consists of 2 mm. of brass and 2.4 mm. of pure gum rubber. The intensity of the filtered radiation at a distance of one centimetre from a point source is taken as 100 units. All other values are relative to this, and direct comparisons can be made, taking the same radium content for each applicator. The intensities given are for points on a line perpendicular to the applicator at its centre. In every case this is the point of maximum intensity.

It will be noted that for points close to the applicator there is a marked difference in the intensity depending on the size of the applicator. But for points at a distance of several centimetres the variation from one applicator to another (and from the theoretical point source) is not so large, and becomes negligible for points at greater distances. It should be noted, also, that the larger the applicator is, the farther is the point for which the intensity is approximately equal to that of the theoretical point source at the same distance. Thus for a square 2×2 cm. practical equality is reached at a distance of 5 or 6 cm.; while for a 10×10 cm. square the difference from the point source value of the intensity is still considerable at a distance of 10 cm.

With the figures of Table VI we are able to calculate the skin erythema doses in milligram hours for different applicators, *provided we know the dose for one*. As an example let us take for this standard a rectangular applicator 4×6 cm.

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TABLE VI

Intensity of Radiation at Different Distances from Various Gamma Ray Applicators

Total Filtration: 2 mm. Brass + 2.4 mm. Rubber

Distance cm.	Point Source	Tubes—Length			
		1 cm.	1.5 cm.	2 cm.	4 cm.
1.0	100.0	92.5	85.0	77.8	54.4
1.5	44.5	42.7	41.2	39.1	30.4
2.0	25.0	24.5	23.8	23.1	19.4
3.0	11.1	11.0	10.8	10.7	9.8
4.0	6.2	6.2	6.1	6.1	5.8
5.0	4.0	4.0	4.0	4.0	3.8
6.0	2.8	2.7	2.7	2.7	2.7
7.5	1.8	1.8	1.8	1.8	1.8
10.0	1.0	1.0	1.0	1.0	1.0

	Circles—Diameter					
	1 cm.	2 cm.	4 cm.	6 cm.	8 cm.	10 cm.
1.0	88.9	68.5	39.4	25.0	17.0	12.4
1.5	42.0	36.7	25.0	17.4	12.8	9.6
2.0	24.2	22.0	17.1	12.8	9.9	8.7
3.0	10.9	10.4	9.1	7.6	5.9	5.2
4.0	6.2	6.0	5.6	4.9	4.2	3.7
5.0	4.0	3.9	3.7	3.4	3.1	2.8
6.0	2.8	2.8	2.7	2.4	2.3	2.1
7.5	1.8	1.8	1.8	1.7	1.6	1.4
10.0	1.0	1.0	1.0	1.0	0.9	0.9

	Squares—Length of Side					
	1 cm.	2 cm.	4 cm.	6 cm.	8 cm.	10 cm.
1.0	84.0	63.5	36.5	23.3	16.0	11.6
1.5	41.5	34.5	23.3	16.2	10.0	9.0
2.0	23.9	21.0	15.9	11.9	9.1	7.1
3.0	10.8	10.4	8.6	7.1	5.9	4.8
4.0	6.1	6.0	5.2	4.4	4.0	3.4
5.0	4.0	3.8	3.6	3.2	2.9	2.6
6.0	2.8	2.7	2.6	2.3	2.1	2.0
7.5	1.8	1.8	1.7	1.6	1.4	1.3
10.0	1.0	1.0	1.0	0.9	0.9	0.9

	Rectangles—Lengths of Sides					
	1 x 1.5 cm.	2 x 3 cm.	4 x 6 cm.	6 x 9 cm.	8 x 12 cm.	10 x 15 cm.
1.0	81.0	55.2	28.4	16.4	10.9	7.8
1.5	40.0	31.9	19.1	12.6	8.7	6.2
2.0	23.6	20.2	12.4	9.7	7.1	5.3
3.0	10.8	1.0	8.0	6.1	4.8	3.9
4.0	6.1	5.9	5.0	4.2	3.4	2.9
5.0	4.0	3.8	3.4	3.0	2.6	2.2
6.0	2.8	2.7	2.6	2.2	2.0	1.8
7.5	1.8	1.8	1.7	1.6	1.4	1.3
10.0	1.0	1.0	1.0	0.9	0.9	0.9

placed at a distance of 3 cm. from the skin, in which case the erythema dose is 2200 milligram hours. From the table we find that the intensity value for this applicator at this distance is 8.0. We now wish to calculate the erythema dose for an applicator 8×12 cm. placed at a distance of 10 cm. from the skin. The intensity value under these conditions is 0.9 according to Table VI. Therefore the erythema dose for the new applicator will be $2200 \times \frac{8.0}{0.9} = 19,600$ milligram

hours. Again for a tube 1.5 cm. long, placed at a distance of 2 cm. from the skin, the intensity value is 23.8 and the erythema dose is $2200 \times \frac{8.0}{23.8} = 740$ milligram hours. The doses

for the applicators of these examples check closely the doses determined empirically from clinical experience.⁹ Considering the method employed in the determination of Table VI (which we cannot discuss fully here) we are able to state that in general skin doses calculated in this manner will have a negligible error. But when points very close to large applicators are considered, the calculated doses may be appreciably in error, and therefore they should be regarded only as first approximations.⁸

Referring again to Table VI we find that the intensity values for the point source vary from 100 at the 1 cm. distance to 1 for the 10 cm. distance, in other words, the radiation at 1 cm. is 100 times more intense than at 10 cm. On the other hand, for an applicator 10×10 cm., the intensities at corresponding distances are 11.5 and 0.89 respectively, so that the intensity at 1 cm. is only 13 times larger than the intensity at 10 cm. This shows the more even distribution of radiation when applicators of large area are used. For the treatment of deep-seated tumors this is of great advantage

because the skin, per square centimetre, receives relatively much less radiation than when a point source or small applicator is used. To offset this advantage, however, a larger skin area is irradiated, and the use of large applicators is in effect a modification of the "cross-fire" method. With applicators of large dimensions it is not necessary to place them at as long a distance from the skin as in the case of the point source, (*q.v.*) in order to obtain the same percentage depth dose.

A knowledge of the dose to administer with different applicators to prevent injury to the skin is obviously essential. But a knowledge of the amount of radiation delivered to a deep-seated tumor (or any tumor) is also very important if we wish to correlate radiation doses and effects produced. Due to a number of practical obstacles, however, the accurate determination of the amounts of radiation delivered to different tissue depths by different applicators is very difficult. The problem is not amenable to mathematical treatment, and experimental methods are unsatisfactory in many respects. For instance, ordinary ionization methods are unsuited because the ionization chamber cannot be made small enough to have dimensions which are negligible in comparison to the distances involved in the experiments. This refers particularly to investigations of the distribution of radiation in an absorbing medium (such as water) in the immediate neighborhood of the source. Remembering that radium is generally employed in close proximity to the tissues to be treated the above limitation is very serious. Nevertheless considerable data has been obtained in various ways, and we shall incorporate some here.^{10, 11, 12, 13, 14}

It is generally accepted that water has very nearly the same absorbing power for X-rays and gamma rays as the

average human tissue (whose density does not differ substantially from that of water). For convenience, therefore, water has been used extensively as the absorbing and diffusing medium in experiments relating to the distribution of radiation, particularly X-rays. The usual procedure is to

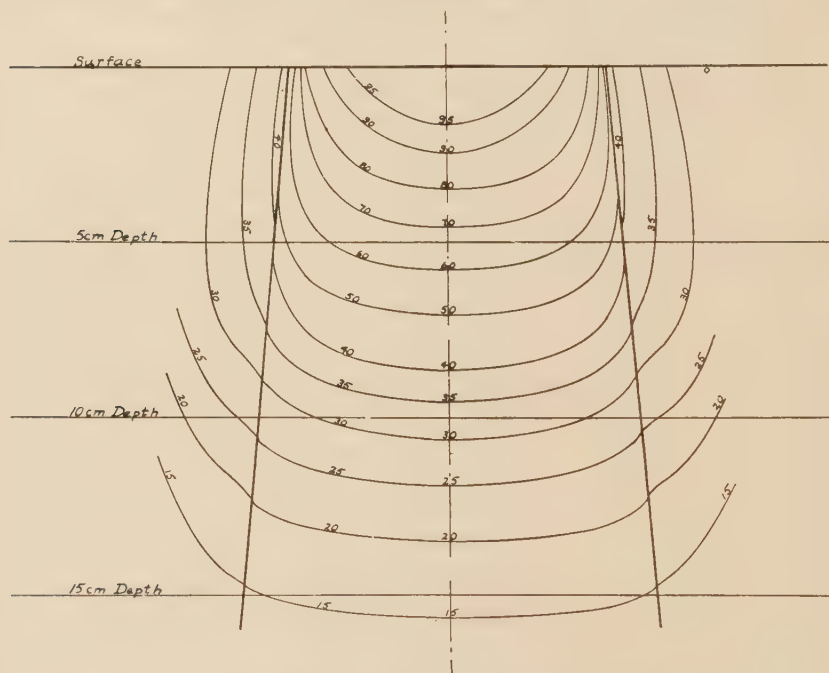


FIG. 11.—Radiation distribution chart for X-rays. Conditions: Water phantom, $35 \times 30 \times 30$ cm.; voltage, 200 K.V. (crest value); filter, 0.5 mm. copper; distance, 50 cm.; field area, 100 sq. cm.

allow a beam of X-rays to “shine” on a tank of water (“phantom”) and to measure the amount of radiation present at different points within the water by means of a very small ionization chamber (having a volume of about 1 cc.). Figure 11 shows a distribution chart for X-rays obtained in this manner. The experimental conditions were: Water phantom $35 \times 30 \times 30$ cm., voltage 200 K.V., filter 0.5 mm.

of copper, distance from target to water surface 50 cm., irradiated area 100 square centimetres. An X-ray machine with closed core transformers, mechanical rectifier, and air-cooled Coolidge tube was used. The chart shows that under these conditions the amount of radiation reaching a depth of 10 cm. along the axis of the beam is 33 per cent. of the amount falling on the surface. It is noteworthy that considerable radiation is found *outside* of the geometrical beam, where the lead diaphragm would cast a "shadow." This is due to the marked scattering of the penetrating radiations by water (*q.v.*).

A similar procedure can be employed to determine the distribution of gamma radiation resulting from the use of certain applicators. As previously mentioned, the size of the ionization chamber limits the applicability of this method to radium sources which are used at a distance of a few centimetres from the skin. We give in Figure 12* a distribution chart for a large radium "pack" consisting of a shallow brass tray 8×12 cm. in which radon tubes are evenly distributed. This pack has a total primary filtration equivalent to 2 mm. of brass, and no lead protection in any direction. When placed at a distance of 10 cm. from the surface of the water in the phantom, the distribution of radiation within the water is found to be as shown in the figure. It is important to note that the lines of equal radiation intensity ("isodoses") have only a slight curvature within the region investigated. This shows that the radiation is fairly uniform at each depth over a considerable distance from the centre. Such a distribution is to be expected, in this case, because the pack has no lead sides tending to limit the radiation to the volume

* This chart was actually determined by a combination of ionization measurements and photographic tests.

directly under the applicator. Using this pack, therefore, a large volume of tissue is irradiated rather intensely.

If we desire to obtain a limited beam, as in the case of X-rays it is necessary to surround the radium with a thick lead wall, since gamma rays are so penetrating that a small

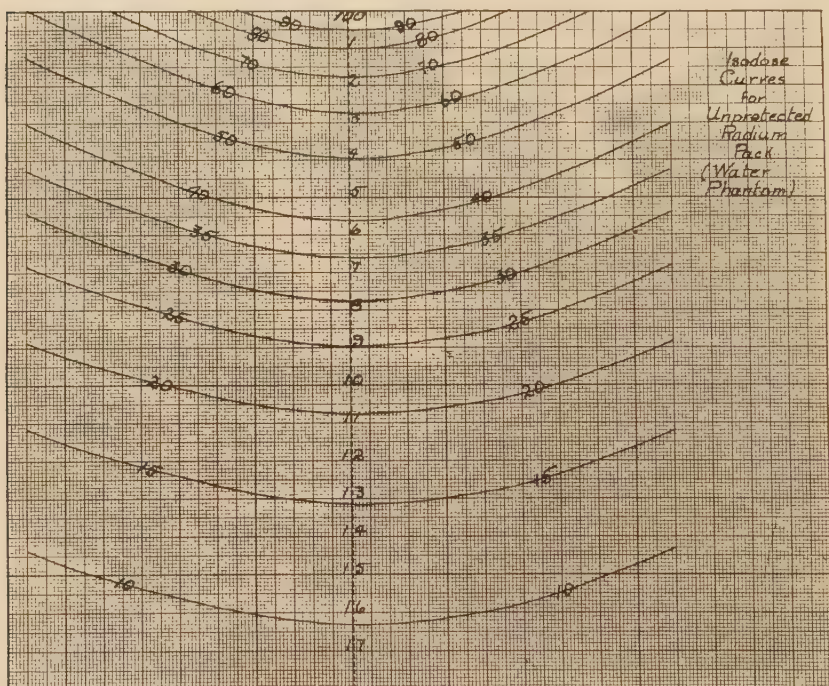


FIG. 12.—Radiation distribution chart for radium pack. Conditions: Water phantom, $35 \times 30 \times 30$ cm.; pack, 8×12 cm.; filter, 2 mm. brass; distance, 10 cm.; no lead to confine radiation.

thickness of lead would have practically no effect. The chart of Figure 13 shows the distribution of radiation for such a beam. The radium container is 7.5 cm. in diameter, the primary filter is 0.5 mm. of platinum and 2 mm. of brass, the lead protection around the radium is 10 cm. thick but tapers down as shown in the upper part of Figure 13. The lines of

equal intensity are much more curved than in the case of the "unprotected" pack (Fig. 12) showing a considerable drop in the radiation from the centre to the edges of the

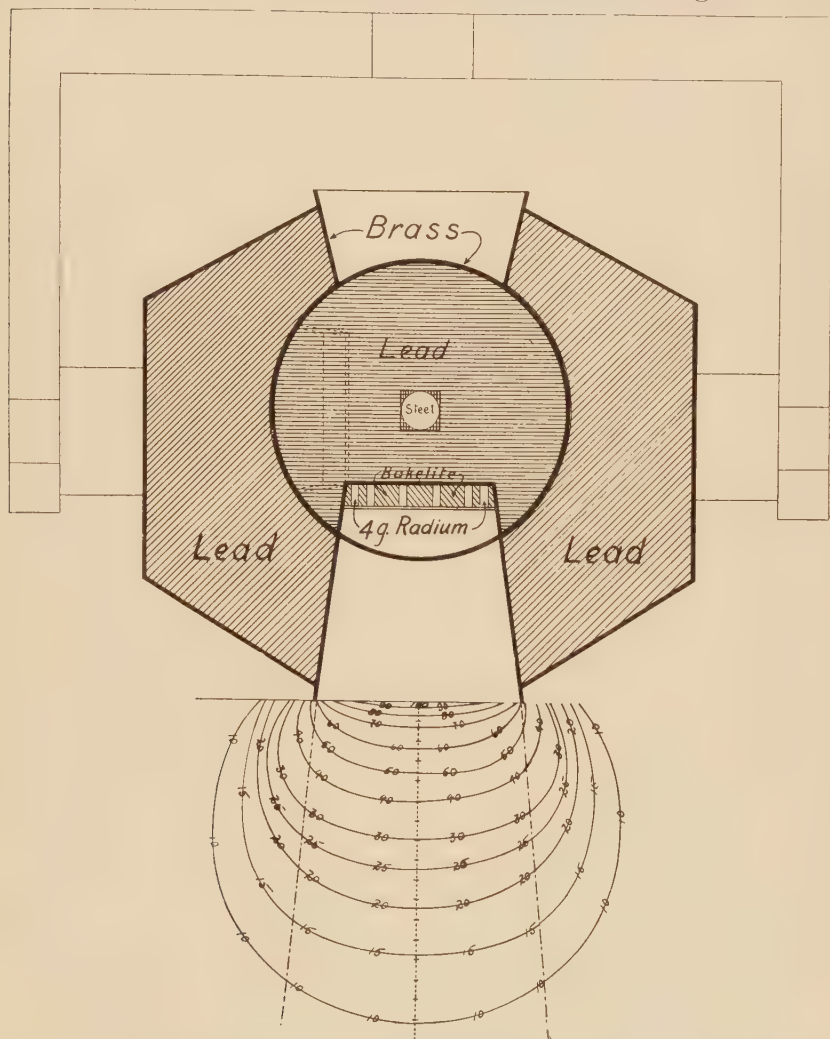


FIG. 13.—Radiation distribution chart for protected radium pack. Conditions: Water phantom, $35 \times 30 \times 30$ cm.; pack, 7.5 cm. diameter; filter, 0.5 mm. platinum and 2 mm. brass; distance, 10 cm.; heavy lead shield as shown.

“geometrical beam.” Furthermore outside of these (imaginary) limits there is a substantial amount of radiation. In this connection we may add that it is impossible to obtain a strictly limited beam of gamma rays or X-rays in a medium such as water, on account of the marked scattering of radiation which is always present. But comparison of the distribution charts for the two packs described above shows that the radiation outside of the desired beam may be reduced effectively by heavy lead screening.

We may consider next the special vaginal applicator, or “bomb” devised by Dr. Harold Bailey.¹⁵ This was designed with the idea of obtaining an intense beam of radiation in a definite direction, limiting as much as practicable the radiation emitted in other directions. The radium or radon is placed in a lead container 3.6 cm. in diameter and 4.2 cm. long. A pocket 1.1×1.6 cm. and 1.5 cm. deep is provided at one end to receive the radio-active material. The filtration in the forward direction is 2 mm. of brass (or more for the tubes which are placed at the bottom of the pocket). Since the pocket is rectangular and the bomb is round, the thickness of lead is greater on two opposite sides than on the other two. In actual use the “bomb” is placed so that the thicker sides are towards the bladder and rectum respectively. The curves of Figure 14 show the distribution of the emitted radiation, the inner curve referring to the narrower cross-section of the beam and the outer to the larger one. It will be noted that at right angles to the main beam the radiation is no less than 40 per cent. of that in the forward direction. Accordingly considerable radiation will reach the bladder and rectum even with this appliance. On account of the limitation of size, the side radiation can be reduced further only by the use of a better absorbing material than

lead, that is, gold or platinum, which would make the applicator very costly.

The curves of Figure 14 give the intensity of radiation

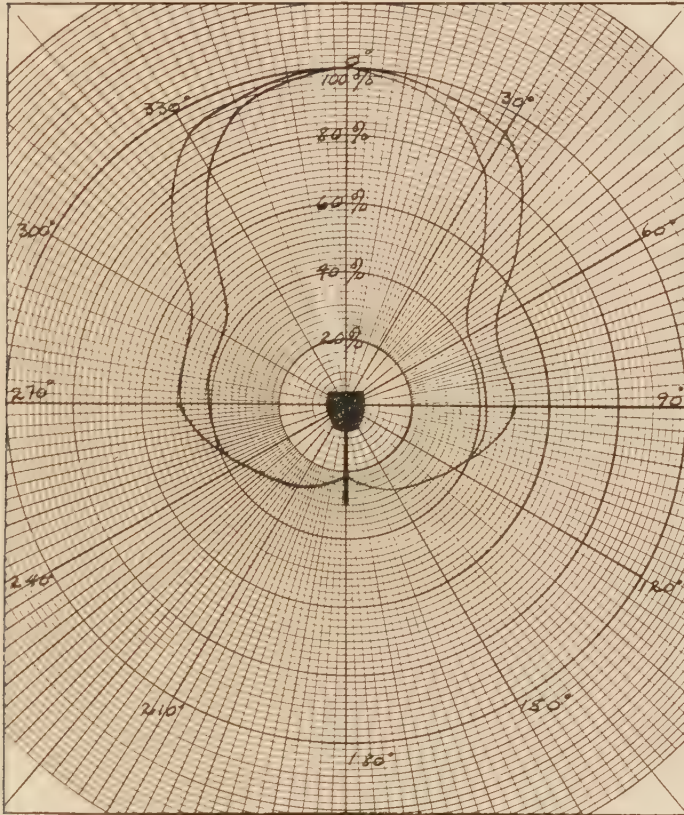


FIG. 14.—Distribution of emitted radiation for "bomb" applicator.

emitted in different directions. If we wish to determine the distribution of radiation in water the problem is much more difficult. The "bomb," being placed in the vagina, is surrounded by tissues, which it is important not to injure severely. It is very desirable to know, therefore, the amount

of radiation delivered to the tissues which come in contact with the applicator. Ionization measurements are not very suitable for this purpose on account of the appreciable size of the ionization chamber, and no other suitable method is available. In view of these difficulties, measurements have been made only for points along the axis of the main beam. The "bomb" was placed approximately in the centre of the water phantom and the 1.cc. ionization chamber at different distances from its face. The results of the measurements are

TABLE VII
*Intensity of Radiation along Main Beam of Bomb Measured
in Water Phantom by 1 cc. Ionization Chamber*

Distance Face of Bomb to Centre of Chamber cm.	Intensity of Radiation Per Cent.
1	100
2	52.7
3	31.6
4	21.4
5	15.4
6	11.5
7	8.9
8	7.4
9	5.8
10	5.0

given in Table VII. The distances appearing in the first column are reckoned from the face of the "bomb" to the centre of the ionization chamber. The radiation intensities in the second column are relative to the value at a distance of 1 cm. taken as 100. The values for the first few points probably do not represent the actual radiation intensities at the points in question, on account of the very rapid drop in radiation which takes place near the source, and the appreciable size of the ionization chamber. But this uncertainty decreases as the distance increases, and the data may be used with considerable assurance for points beyond 2 or 3 cm. By

combining the data of Table VII and Figure 14 it is possible to estimate the relative amount of radiation reaching different points in the tissues which are meant to be protected.

The limitations which have been mentioned in connection with the study of the distribution of radiation in water due to the presence of the bomb apply with more force to the case in which a single radium tube is used as the source. Many attempts^{11, 12, 13, 14} have been made to solve this problem, but the results obtained by different investigators are widely discordant. We shall give here some data which we feel is fairly well suited to the problem at hand, although not free from objectionable features. It has been found that ordinary butter is discolored by radium rays.¹⁶ If a tube of radium is embedded in a block of butter (which is kept on ice) after a certain time, depending on the amount of radium used, the butter immediately around the tube has a snowy appearance, while beyond this region the butter is apparently unchanged. The line of demarcation is quite sharp when it is not too far from the tube, but becomes less well defined with increasing distance. Nevertheless it is possible to measure the discolored region with considerable precision. Evidently it takes a certain minimum amount of radiation before the butter is discolored and the line of demarcation represents the position at which this minimum amount has just been exceeded. Near the source this minimum amount of radiation is delivered in a short time because the intensity of radiation is high, at greater distances a longer time is required. It will be seen then that the time which elapses before the discoloration reaches a certain point is inversely proportional to the intensity of radiation at that point. This gives an indirect means of determining the intensity of radiation at different distances from certain

radio-active sources. For a radium tube 16 mm. long, 4 mm. in diameter, having a filter of 0.5 mm. of platinum, the data thus obtained are given in Table VIII. The intensity values are relative to the one at 10 mm. taken as 100. They refer to points on a perpendicular bisector to the tube. The isodose lines near the tube follow the general shape of the source, but they become practically circular at greater distances.

Ionization measurements cannot be made at points as close to the centre of the tube as 5 or 7.5 mm. However, for

TABLE VIII
*Intensity of Radiation at Different Distances from a Radium
Tube 16 mm. Long, 4 mm. in Diameter, with
0.5 mm. Platinum Filter*

Distance from Centre of Tube mm.	Intensity Per Cent.
5	376
7.5	178
10	100
15	50
20	33
25	25
30	20
40	14
50	11

points at greater distances the results do not differ greatly from those here given. This lends considerable weight to the data obtained by the butter discoloration experiments.*

The data on the distribution of radiation which we have given are intended to assist the gynecologist in choosing the method of attack for a given case. Tubes may be used in the vagina, the cervix, or the uterus, the Bailey "bomb" may

* Space does not permit a critical discussion of the applicability of this method to the determination of the intensity of radiation at different distances from the source. We wish to point out, however, that with the experimental procedure outlined above, the results involve the assumption that a small intensity of radiation acting for a long time has the same effect on the butter as a large intensity acting for a correspondingly short time. Under certain conditions this can be obviated as shown in other publications.^{16, 17}

be employed, and external "packs" or X-rays may be applied. A knowledge of the relative amounts of radiation reaching certain critical points in the possibly invaded field for various possible combinations of treatment may be obtained from these data. Even a casual perusal of the data, however, will show that the radiation at a distance of a few centimetres from any applicator is very much less than at closer range. The effectiveness of radium, therefore, decreases very greatly with the distance. This has led to the burying of the radio-active sources directly into the neoplastic tissues. Two general methods have been employed: (A) Radium or radon needles are inserted into the tissue to be treated, and are withdrawn after a certain length of time. (B) Radon implants are discharged into the tissue and are left in place indefinitely. The second method is possible only because the "life" of radon is relatively short, two weeks sufficing for the disintegration of over 90 per cent. of the initial amount. In a short time these implants lose their activity and become harmless.

At first only very small glass tubes^{18, 19} each containing about one millicurie of radon, were used for permanent implantation. During the last two years, however, glass implants ("bare tubes") have been superseded almost entirely by gold or platinum implants.²⁰ These are preferable on account of the smaller amount of necrosis which they produce in the tissues immediately surrounding them. The radiation emitted by "bare tubes"—glass tube without additional filter—consists mostly of beta rays, and therefore is absorbed to a large extent by a few millimetres of tissue. On the other hand, the radiation emitted by gold implants has been filtered by 0.2 or 0.3 mm. of pure gold, constituting the wall thickness of the container, and very little beta

radiation is present. By sealing radon directly in a gold capillary tube, the dimensions of the implants can be kept small, which is very desirable from the point of view of trauma. A gold implant of 0.2 mm. wall thickness has an external diameter of 0.55 mm. and one of 0.3 mm. wall thickness is 0.75 mm. in diameter. In either case the length is usually about 5 mm.

Radium or radon needles which are employed for temporary implantation^{21, 22, 23, 24, 25} may be of any desired

TABLE IX
Comparison of Necrosis Produced by Unfiltered and Filtered Radon Implants
Necrosis (Complete and Partial)

Radon Content mc.	Glass Tube		0.2 mm. Gold Tube		0.3 mm. Gold Tube	
	Radius mm.	Volume Per Cent.	Radius mm.	Volume Per Cent.	Radius mm.	Volume Per Cent.
0.5	2.0	30	1.0	3.7	0.8	1.9
1.0	3.0	100	1.6	14.8	1.14	5.5
1.5	3.6	174	2.1	34.5	1.5	12.6
2.0	4.1	255	2.5	57.8	1.8	21.5
2.5	4.4	315	2.8	81.5	2.1	34.5
3.0	4.6	360	3.0	100	2.3	45.0
4.0	5.0	460	3.4	146	2.7	73.0
5.0	5.3	550	3.6	173	3.1	110
7.0	5.6	650	4.0	237	3.5	163
10.0	5.9	760	4.5	340	4.1	253

length. Ordinarily, however, the active part is between one and two centimetres long. The filtration should be sufficient to remove most if not all of the beta radiation. In such cases the distribution of radiation in the tissues surrounding a needle is not far different from that due to a radium tube. The figures of Table VIII therefore can be used in this connection also. In the case of radon implants we are chiefly concerned with the effect produced at a short distance from the source and with the amount of tissue necrosis which develops. Comparative information relative to this is given

in Table IX for glass and gold implants.¹⁷ The experiments which supplied the data were made on the dorsal muscles of rabbits and therefore the necrosis observed was produced in this type of tissue.

As already mentioned, the effect of radon implants (whether glass or gold) is primarily local, and therefore the *spacing* of the sources within the tumor mass is of the utmost importance. The success of the treatment depends in a large measure on the effective irradiation of every portion of the tumor. If this is to be done with a minimum amount of radon and the least gross destruction of tissue, the implants must be distributed throughout the volume so as to insure sufficient radiation at every point in the mass without unnecessary overlapping. In practice this is extremely difficult to do, and we may be sure that in cases where good final results were obtained the amount of radon used was considerably in excess of the theoretical minimum. In other words too much reliance should not be placed on the local effect of each implant, but the total amount of radon should be adjusted so as to insure sufficient irradiation of the tumor tissue, on the assumption that the spacing of the individual implants is probably incorrect. What allowance is to be made for this source of error depends largely on the judgment and experience of the operator. What we wish to emphasize here is that the dose calculated on the basis of the volume of the tumor and the radius of action of each implant is almost always too low to obtain a good permanent result. As a corollary of what we have said, it follows that in the ultimate analysis chief reliance must be placed on the combined gamma radiation of all the implants used. The beta radiation, being easily absorbed by tissues, is effective only in the immediate neighborhood of the implant. Since

the gamma radiation is also more intense near the sources, it is evident that the beta radiation is superfluous. Furthermore, it is objectionable on account of the intense local necrosis which it produces. This shows why filtered implants (gold or platinum) are much to be preferred.

SOME BIOPHYSICAL CONSIDERATIONS.—The data which have been given in the preceding paragraphs refer to the dose of radiation delivered to a given point in the irradiated tissues. What effect or effects the radiation produces is a question which is outside of the field of physics. We may, however, discuss briefly some problems from the biophysical point of view, primarily for the purpose of calling attention to the importance of what we may call the “susceptibility ratio” of different tissues.

Radiologists differ as to the actual process which brings about the retrogression and ultimate disappearance of a tumor following radiation treatment. It is generally recognized, however, that both the effect on the tumor and the effect on the surrounding normal tissues must be taken into account. It is well known, also, that all living cells do not exhibit the same susceptibility to radiation. Accordingly in radiation therapy we have to deal with a *differential action* of radiation. That is, equality of dose does not necessarily mean equality of effect in all tissues, and in fact, in some cases the same dose will influence very markedly one type of tissue but will have no perceptible effect on another. It would seem that the desideratum in radiation therapy is to adjust the dose and administer the radiation in such a way that the tumor will be caused to retrogress without serious injury to the surrounding normal tissues and the patient as a whole. To do this we must study how the relative susceptibility of tumor and normal tissues (including the patient

as a whole) may be varied—if it is possible to do so. In order to crystallize our ideas let us assume two types of tissue A, and B, having radiation susceptibilities S_A and S_B respectively. The relative susceptibility of the two tissues may then be expressed as a ratio $\frac{S_A}{S_B} = R$, and we may call this the “susceptibility ratio.” If A is a tumor and B the surrounding normal tissue, the larger is R the more susceptible is the tumor with respect to its surrounding tissues, and the simpler becomes the problem of treating the patient. If in any particular case it is possible to influence favorably this ratio by any means at our disposal it is evidently desirable to do so. Accordingly we shall consider now some means by which it may be possible to change the susceptibility ratio.

In the first place we wish to point out that the question of improving the distribution of radiation within the irradiated tissues is outside the present problem. Naturally the larger the dose delivered to the tumor the more marked will be the effect. Therefore the mode of application should be adjusted to deliver the maximum amount of radiation to the tumor and a minimum amount to the surrounding normal tissues, *in so far as practical considerations will permit*. It will be seen, however, that no matter what the distribution of radiation is, the dose is substantially the same for the tumor and normal tissues *at the line of demarcation*. In other words, on the periphery of the tumor we have normal and neoplastic tissues in actual contact and even intermingled. Therefore, whatever radiation reaches the one will necessarily reach the other. The success of a treatment probably depends largely on the dose which is delivered to these critical points in the tumor, irrespective of the dose which may be delivered to the centre of the tumor. For instance, when needles or implants

are placed in the tumor, the dose in the centre, and even throughout the bulk of the tumor, may be very large, but outside of the apparent periphery, where infiltration may be present, the dose is limited by the injury to the normal tissues which is deemed permissible. It will be seen, therefore, that even under the best conditions of radiation distribution the relative susceptibility of the tissues is of paramount importance.

How can we influence the susceptibility ratio? We have just eliminated the question of distribution, first because intrinsically it has nothing to do with susceptibility, and then because in the ultimate analysis we have to deal with the effect of the *same* amount of radiation on different types of tissue. From the factors which define a radium treatment, therefore, we may strike out for our present purposes those whose influence is *only* on the distribution of radiation (*i.e.*, the distribution of the source, the distance or spacing, the geometrical configuration of the tissues, the absorbing power of the tissues). The filtration affects the distribution of radiation, but it also changes the quality, which may modify the susceptibility ratio. Let us consider this first.

It will be recalled that the greater the filtration the more penetrating the radiation is, and therefore the more will reach the deeper layers of tissue for the same surface dose. Also, other conditions being equal, the farther from the surface the radium is applied, the greater will be the *relative* depth dose. It is evident, then, that within limits, we may obtain essentially the same depth distribution of radiation in (at least) two ways: (1) by using low filtration and a long distance, and (2) by using high filtration and a shorter distance. (In either case, of course, filtration and distance must be properly adjusted to obtain this equality.) Which combi-

nation should be used in any particular case? *Assuming* that the quality of radiation has no influence on the susceptibility ratio (or ratios) the answer is very simple: Either combination is biologically as effective as the other, but in general, one is more economical than the other,* and therefore is preferable from a practical standpoint. However, this assumption is not justified. The present knowledge of the biological action of radiation does not permit us to say definitely that the susceptibility ratio is or is not independent of the quality of the radiation. But in the absence of conclusive evidence one way or the other, it is the part of wisdom to bear in mind that the quality of radiation may influence the susceptibility ratio of normal and pathological tissues. This will help in the interpretation of results when different types of radiation are employed. It should be noted, however, that in order to attribute any observed differences in the results to the difference in the quality of radiation, all other factors must be the same. This is the chief difficulty in drawing conclusions from clinical work, and it may be safely stated that this problem will not be definitely solved by clinical observations.

The question of the possible influence of the quality of radiation on the susceptibility ratio is of particular importance in deciding whether a deep-seated tumor should be treated by X-rays or gamma rays (externally applied). For this purpose large amounts of radium must be used in order to obtain a depth distribution of radiation comparable to that obtained with high voltage X-rays. From the economical standpoint, therefore, X-rays are preferable provided the same results can be obtained as with radium "packs." Com-

* Which one is more economical depends on the particular case under consideration, and no general conclusion can be given here.

paring the distribution charts given in Figures 11 and 13 for high voltage X-rays and probably the largest radium pack which it is practical to use, we find that the depth doses are

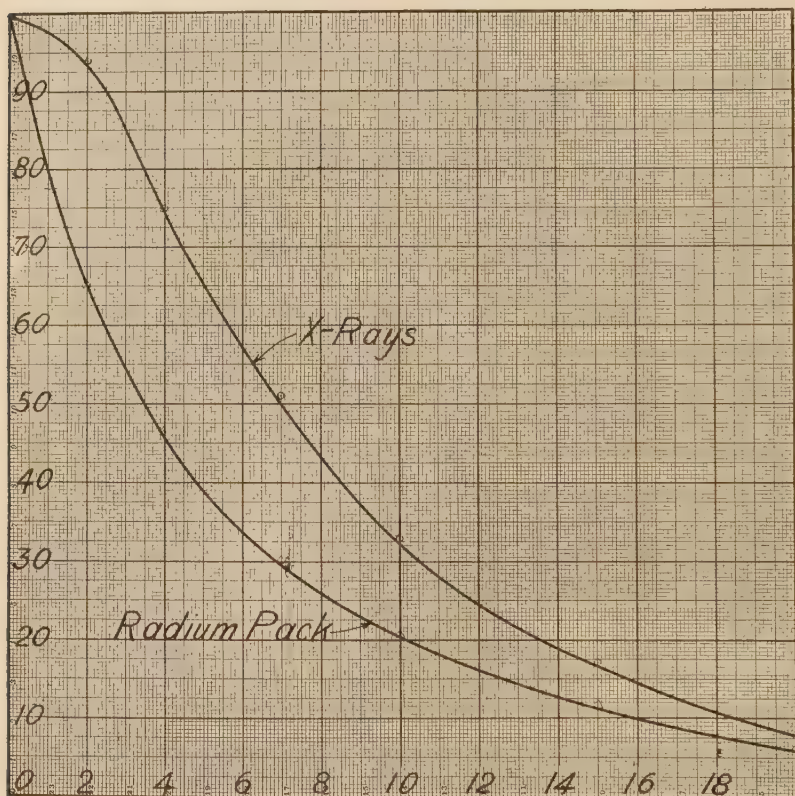


FIG. 15.—Comparison of depth doses for high voltage X-rays and radium pack. (Conditions as stated in Figures 11 and 13.)

higher for the X-ray than for the pack treatment. This is shown more clearly by the curves of Figure 15. For instance, at a depth of 10 cm. the X-ray intensity is 33 per cent. and the gamma ray intensity is 22 per cent. of the intensity at the surface. In either case the absolute depth dose is limited by

the possibility of injury to the skin, and for the same skin effect, we may take 33 and 22 units, respectively, as the absolute amounts of radiation reaching a depth of 10 cm. If a tumor at this point is to be influenced to the same or a greater extent by 22 units of gamma radiation than by 33 units of X-radiation, then its susceptibility to gamma rays must be correspondingly greater. If we prefer to think of the retrogression of a tumor as due to the setting up of a favorable reaction in the normal tissues, we still have to assume a different tissue susceptibility for X-rays and gamma rays. Accordingly the concept of a "susceptibility ratio" simplifies the analysis of such problems. Irrespective of the mechanism of the biological or therapeutic action of radiation, if the susceptibility ratio varies with the quality of the radiation we have a good criterion for the determination of the most effective radiation. This can be done by biophysical experimentation and then checked by clinical observations.

At this point we may call attention to the fact that in the radiation treatment of a tumor there is really not one, but, in general, a large number of susceptibility factors involved. There is a susceptibility ratio for each pair of cells which are different—whether the difference is in type, age, etc. For instance, in the treatment of a deep-seated tumor the susceptibility ratios between skin and tumor tissue, skin and blood vessels around the tumor, skin and blood, tumor tissue and surrounding normal tissues, are all involved and are important. If these ratios change with the quality of radiation and we know how they change we can select the radiation which is best adapted for the treatment of the particular patient under consideration. If they do not change then one type of radiation is as good as another, and the only

criterion for selection is the distribution of the radiation which can be obtained with the different types of rays and the possibilities of application.

The quality of radiation is one factor which may influence the relative susceptibility of tissues, that is, the susceptibility ratio. We shall consider now some factors which are involved in the mode of administration of the radiation. As previously stated this refers particularly to the time spacing of the treatments and therefore there is really one factor involved,—*time*—but the intensity of radiation is also involved indirectly. It is well known that radiation treatments may be long or short, and may be repeated at different intervals. Sometimes the length of the treatment is more or less fixed by the amount of radium available, and in the case of radon implants it is fixed by the life of radon. But in general it is possible to vary the time within wide limits if it is desirable to do so. Also there are no serious difficulties in the use of fractional treatments extending over a considerable period of time. The question, therefore, is to determine the mode of administration of the radiation which will yield the best results in a given type of case. The solution of this problem by clinical observations is again very difficult, which accounts for the wide differences of opinion among radiologists. We wish to point out that here also it is largely a question of the variation of the susceptibility ratio—with respect to the time element of the treatments. Again the problem can be solved by biophysical investigations.

The usefulness of the concept of a susceptibility ratio in the analysis of radiation problems will be brought out clearly by the following example: It is often asserted that better results are obtained by fractional treatments than by the so-called massive (single) treatment method. The reason

given is usually that "more radiation can be administered to the tumor in this way." That is, the sum of the doses given over a period of time is larger than the dose which the skin permits to be given at one sitting. Irrespective of whether better results are or are not obtained by one method or the other, the "reason" given is certainly wrong. For, it is not a question of the dose which can be delivered, but the effect which it will produce. With the fractional treatment method the total tumor dose is larger, but the skin dose is also larger *in exactly the same proportion*. This larger dose does not produce a more marked skin effect but the implication is that it is more effective on the tumor. If this is to be the case, then the mode of administration of the radiation must affect the relative susceptibility of the skin and the tumor. For, the percentage radiation which reaches the tumor is exactly the same irrespective of the time factor, and the difference in response can only be due to a difference in the relative susceptibilities of skin and tumor, other normal tissues and tumor. Therefore, analyzing the problem from the point of view of the possible influence on the susceptibility ratios we cannot overlook the question of the relative effectiveness of the radiation on different tissues, which in reality forms the true criterion.

The preceding brief discussion shows that *dose* and *effect* are really inseparable, and that from the very nature of radiation therapy we must always deal with many effects. This multiplicity of effects is responsible for the advantages and difficulties of radiation therapy. If radiation is used as a means for the gross removal of a tumor by its "caustic" action, it is little better than surgery. On the other hand, if by proper adjustment of conditions, we can bring about a differential action of radiation whereby a deleterious effect

is produced in the tumor and a reaction opposing cancer growth is set up in the surrounding normal tissues, radiation therapy is much superior to surgery. Experience has shown that such a favorable state of affairs does exist in some cases. The progress of radiation therapy will depend on the determination of the conditions which influence favorably the differential action of radiation. Many possibilities exist in the proper control of the irradiation factors—quality of radiation, duration of a continuous treatment, divided treatments, etc. But the territory to be explored becomes very vast when we consider the combination of radiation with other agents—physical, chemical, etc. Already there is some evidence, although more suggestive than certain, that colloidal lead influences favorably the relative susceptibility to radiation of tumor and normal tissues. Many years will elapse before sufficient quantitative data will have been obtained to formulate definite biophysical relations about the action of radiation on living matter. Whatever influence these researches may have on the use of radiation in cancer therapy, the results will be of great scientific value. In radiation we possess a means of influencing life phenomena without the introduction of external material agencies, and such studies cannot fail to throw some light on the mechanism of the living cell.

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CHAPTER III

THE PATHOLOGY AND ACTION OF RADIUM

THE action of radium varies considerably under different conditions and is influenced by many factors. An extensive literature has developed and a number of monographs on this subject have appeared. The effect of radium upon various microorganisms is important, bearing, as it does, so directly upon the mooted question of the advisability of preoperative irradiation. Chambers and Russ¹ found that emulsions of *staphylococcus pyogenes aureus*, *bacillus coli communis*, *bacillus pyocyaneus*, *bacillus anthracis* and *bacillus tuberculosis*, could be sterilized by radium emanations. It has been shown that radium emanation possesses considerable bactericidal properties when used at a concentration of 0.5 millicurie per c.cm.

For clinical purposes this is very strong dosage. It would seem that for practical clinical purposes, the bactericidal effect of radium is of little value, and it is questionable whether the destructive action of the rays upon the tissues does not produce devitalizing effects that would, in ordinary dosage, more than counterbalance the bactericidal properties of the emanations. Jansen,² Strassman,³ Goldberg,⁴ Omeliansky⁵ and others have done considerable work upon this subject.

Halberstraedter⁶ demonstrated that radium irradiation destroyed the power of reproduction of trypanosomes, but did not affect their motile power, and that infection by them remained unchecked. There is no doubt that the lower forms of animal life can be destroyed by radium irradiation, but it still remains to be proved that it is capable of destroying

the organism within the human body without inflicting undue injury to or causing destruction of adjacent tissue.

The action of radium upon normal tissue has been the subject of considerable study. Colwell and Russ,⁷ in their monograph, devote 112 pages to this subject alone.

THE EFFECT OF RADIUM ON THE VARIOUS TISSUES

THE SKIN.—The effect of radium irradiation upon the skin is of the utmost importance, as this is the portal of entry for many forms of radiotherapy. It is upon the skin effect that the dosage is based. The skin reaction is generally divided into four degrees of severity: (1) simple erythema; (2) erythema followed by degeneration; (3) vesication and superficial ulceration; (4) deep ulceration. The reaction generally appears in about ten days, although secondary reaction may occur in from one to two months. When ulceration occurs, healing is slow, and months are often needed to effect a cure.

THE BLOOD.—Irradiation results in a temporary increase in the red and white blood-cells; this is followed by a more or less pronounced leukopenia. Prolonged or repeated exposures result in anemia. This blood reaction is of great clinical importance. Periodic blood examinations should be made upon all those working with radium or the X-rays.

THE SPLEEN.—Irradiation produces an increase in the connective tissues, destruction of the lymphocytes, and diminishes the cellular elements of the blood. Small hemorrhages are of frequent occurrence. In addition to these effects the bone-marrow, lymphatic glands and solitary follicles exhibit a diminution of lymphatics and an accumulation of the red blood corpuscles; here and there scattered hemorrhages are present. Phagocytosis of red cells also occurs.

THE BLOOD-VESSELS.—The endothelium of the blood-vessels is quite susceptible to the action of radium. Swelling and proliferation of these layers occurs, and finally, if the dosage has been sufficiently large, thrombosis and subsequent permanent obliteration of the lumen take place. The muscular coat of the arteries is moderately resistant.

THE MUSCLES, both voluntary and involuntary, are fairly resistant, but under prolonged irradiation they may be converted into fibrous connective tissue, a fact that has been demonstrated by Lacessagne⁸ and others.

CONNECTIVE TISSUE.—Yellow elastic tissue is extremely resistant to the action of radium, whereas white tissue appears to undergo swelling, degeneration, and finally, destruction.

HYALINE CARTILAGE.—According to Colwell and Russ⁹ the initial change appears to be one of destruction. This subsequently gives place to a marked hypertrophy of the cartilage substance.

THE NERVOUS SYSTEM.—The experiments of Horsley and Finge¹⁰ appear to demonstrate that the nervous system is relatively unsusceptible to the action of radium, and that many of the destructive changes described by the earlier investigators were the result of the action of the element upon the vascular system and artefacts due to operative intervention incident to the application of the radium.

Horwitz¹¹ found a diminution of the chromatin of the nerve-cells and a thickening of the fibres. Small doses of unfiltered radium embedded in the brain, produced a localized area of necrosis surrounded by a zone of inflammatory reaction. It would appear that small doses of radium applied to the brain over a moderately long period produce the effects stated with comparatively slight neurologic disturbances,

but that large doses applied for a short time result in pronounced neurologic changes and finally in a fatal result. (Bagg, Ewing and Quick.¹²)

THE UTERUS AND OVARY.—The effect of radium upon the ovary is of the utmost importance. The almost uniformly satisfactory results following irradiation for the relief of hemorrhages, such as those produced by benign uterine growths, as for example, myomata, are well known. The results obtained by this method of treatment suggest an internal castration, and are similar to those following a bilateral oöphorectomy.

Taking as a standard dosage 1200 mg.h., this, applied within the uterus, will check all bleeding, usually almost immediately, although in a small proportion of cases bleeding may continue for a few weeks. This cessation of flow is followed by the symptoms that accompany the artificial menopause, and in about the same proportion of patients, and of the same severity as would occur after a bilateral oöphorectomy. The question then arises, are these effects produced by the action of radium upon the ovary, the uterus, or if a tumor is present, upon the neoplasm or upon two of these or all three?

There is no question but that there is a local action upon the inner surface of the uterus, but the important question should be raised whether this local action is sufficient to account for the resulting symptoms, even if we accept the theory that the endometrium possesses endocrine properties that act independently of or in conjunction with the endocrinal properties of the ovaries, the clinical results are still open to considerable doubt. We have examined numerous uteri that have been subjected to radium irradiation, and may summarize these findings as follows:

Radium produces a distinctly local macroscopic and histologic change that is similar in general character to the change produced by irradiation elsewhere, but is modified somewhat by local conditions. A localized sloughing or necrotic area is present, and this may, and generally does, involve the proximal layers of the myometrium, especially in those cases in which a moderately thorough curettage has preceded the irradiation. This area may be more than 5 cm. in length and 1 to 1.5 cm. in breadth, but is generally considerably smaller. The area of necrosis is surrounded by a zone of inflammation. This reaction may be seen upon the anterior and the posterior uterine wall. It is usually much more marked upon the posterior wall, probably owing to the fact that, during the irradiation, most patients spend a large part of their time upon their backs.

In many cases no macroscopic evidence of irradiation is present upon the anterior wall, but histologic examination rarely fails to demonstrate such an area if a similar lesion is found upon the posterior wall of the endometrial cavity. The area of necrosis heals slowly, often persisting for weeks or even a few months. This corresponds in duration to what is known concerning similar radium reactions upon portions of the body where they can be observed more accurately, as for example, upon the skin.

These findings account for the fact that patients treated by intrauterine irradiation not infrequently develop a persistent leukorrhea. In many cases intrauterine reaction is less marked, and an effort to check up on these cases shows that the leukorrhea had been less pronounced. In the great majority of cases an examination, made two months or more after the treatment, disclosed little or no macroscopic evidence of the irradiation. Difficulty is generally

experienced in selecting the site from which to secure histologic specimens.

Despite the lack of either macroscopic or histologic evidence of irradiation in the uterus some months after the treatment, the amenorrhea is generally permanent. The authors have examined many uteri in which, even after careful histologic examination, they were unable to demonstrate any evidence of previous irradiation. In none of the uteri that they examined were massive cicatrices present. The stroma of the endometrium at the site of the irradiation is often somewhat denser than normal, but not more so than is often observed in the non-irradiated specimens. A localized fibrosis of the myometrium at the site of previous irradiation is also observed at times, but these changes may be absent. When, however, they are present, they are distinctly localized and generally moderate in degree.

Blood-vessel changes have been greatly emphasized as factors in the production of amenorrhea, and whereas radium may cause obliteration of the blood-vessels, such changes being observed in uteri in the immediate neighborhood of the irradiated site, these are generally quite localized and not usually a prominent feature of the histologic picture. The same is true of the blood-vessels of uterine myomata which have been subjected to irradiation.

Thromboses of the smaller uterine blood-vessels and of those supplying uterine myomata are not uncommon in uteri that have not been subjected to irradiation, especially if the patients have attained or are approaching the menopause. In none of the specimens examined by the authors have the alterations been of such a character as would seem likely materially and permanently to affect the menstrual function.

OVARY.—In 1913 Haendly¹³ reported the destruction of all primordial follicles in a specimen the uterus of which had been subjected to intensive irradiation by mesothorium and X-ray.

Numerous experiments have been performed for the purpose of determining the effect of radium upon the ovary. Forsdike¹⁴ reports the results secured in a series of experiments. This investigator states that, with strong doses of irradiation, when the radium is brought into direct contact with the tissue, the effects are manifest in a few hours. With moderate doses there is a definite quiescent period before any change is observed, but the microscopic changes are, nevertheless, identical, though delayed.

Apart from the engorgement of vessels and hemorrhages, the primordial follicles are the first to be affected. Later the cytoplasm of the cell becomes altered, but the cell is probably destroyed by the action upon the nucleus. Horwitz's¹⁵ experiments upon rabbits were followed by atrophy of the Graafian follicles. Pinch¹⁶ voices the opinion that the Graafian follicle is extremely susceptible to irradiation. Matthews and others have shown that the ovaries are more susceptible in mature animals than in those of the young. The authors have examined a number of ovaries taken from patients who had been treated for benign hemorrhages by irradiation, and the effect of the treatment, even when the irradiation had been performed a year or more previously, was always present and manifested by absence of the primordial, Graafian follicles and the corpus luteum.

A similar picture is presented in ovaries secured by post-mortem from patients who had been treated with radium for carcinoma. In those ovaries secured by operation from cases in which irradiation had been performed for benign hemor-

rhage, and in which the treatment had failed to check the bleeding, or in which a period of amenorrhea had been followed by a recurrence of hemorrhages, active follicles in various stages have nearly always been observed. The authors attribute these findings to failure adequately to irradiate the ovary. They believe, therefore, that the success attained by intrauterine irradiation by radium is due mainly to the action of the radium upon the ovary and the effects upon the uterus are of secondary importance. This is borne out clinically by the occurrence of the artificial menopause and by the presence of active follicles in the ovaries in patients upon whom irradiation has failed to produce an amenorrhea. The postirradiation atrophy of myomata can probably be explained by a deficiency of the ovarian hormone. In the early days of abdominal surgery a similar shrivelling of the tumor was frequently observed to follow a bilateral oöphorectomy.

It has been stated elsewhere that small doses of radium produce a stimulation of the ovarian function. Geller¹⁷ states that, after weak irradiation of the ovary in rabbits, the histologic picture showed no positive signs of stimulation, but in almost every case degenerative changes were evident in the ovaries and follicles in all stages, without manifestation or predilection for the ripe follicles. Biedl¹⁸ has demonstrated that transplants made of irradiated ovaries are doomed to certain and rapid destruction.

MALIGNANT NEOPLASMS.—That radium will destroy any if not all forms of malignant cells has definitely been proved both by experimental work and by clinical observations. This statement presupposes that the cell has been properly irradiated. The inability to apply a lethal neoplastic dose to all the cells generated by a given tumor explains the failure to

secure complete results. The neoplastic tissue is destroyed and replaced by fibrous connective tissue. The method by which this destruction of the malignant cells is accomplished is not known, although numerous theories to explain the process have been advanced.

After repeated studies, Bergonie and Tribondeau¹⁹ were led to make the following generalized statement, which became known as the Law of Bergonie and Tribondeau. Immature cells and cells in an active state of division are more sensitive to irradiation than those cells that have already acquired their fixed adult morphologic and physiologic characters. This is particularly true of those tumors composed of lymphoid cells. In general, therefore, tumors that are made up of a large proportion of embryonal cells are more susceptible to irradiation than are those in which the constituents are mainly adult types of tissue.

As a general rule, the more undifferentiated the cells are, the more malignant is the tumor. Furthermore, tumors that grow rapidly are, as a rule, more malignant than are those that grow slowly. Tumors increase in size by cell division; cell division is, therefore, generally speaking, more marked in the intensely malignant forms of neoplasm. Numerous efforts have been made to correlate the histologic appearance of neoplasms with their susceptibility to irradiation. Especially noteworthy in this respect is the work of Ewing.²⁰ The effects produced by irradiation on neoplastic tissue vary with and are affected by the type of treatment and the character of tumor. Following the application of radium different histologic pictures are presented at varying intervals. These histologic changes are too well known to require a detailed description here.

The first effects of radium are characterized by inflamma-

tion: there is swelling of the nucleus of the malignant cells, degeneration, breaking down of the nuclear capsule, swelling of the cell proper, fragmentation of the nucleus, breaking down of the cytoplasm, hyperchromatosis, vacuolization and hydropic swelling. Nuclei undergoing mitosis are especially susceptible and cell division is checked soon after irradiation. The chromosomes split, the spindle threads disintegrate and the cytoplasm undergoes rapid destruction. While these changes are taking place the stroma becomes edematous and hyperemic.

A leukocytic infiltration is present. New capillaries appear and numerous fibroblasts develop. As the neoplastic cells break down, a large part of the chromatin is absorbed or accounted for by the leukocytes. The chromatin forms into various-sized masses, some of which are quite large; these are found squeezed between the interstices of the newly developing fibrinous connective tissue. These masses of chromatin, due to pressure and the action of the leukocytes, assume irregular shapes, at times simulating giant cells. Indeed, the term "irradiation giant cells" is a descriptive one. At other times the masses of chromatin resemble syncytial cells, and in some cases the arrangement and appearance of the irradiated tissue suggests a miliary tubercle.

Tumor cells closely associated with blood-vessels are less susceptible to the action of radium. The stroma cells may, to a less marked degree, exhibit the irradiated characteristics of the neoplastic tissue, but, as Ewing observes, "the ideal radium therapy seems to require a nice adjustment of relation between destructive effect on tumor cells and stimulation of stroma cells." The destruction of the tumor cells resembles an autolytic degeneration. The manner in which the changes in the tumor cells are produced is still in doubt.

The chemistry of irradiated cells is also still undetermined. Ewing declares that the cell constituents appear ionized and the intercellular ferments activated, so that reaction readily occurs, which would not otherwise take place. If this theory is correct, it is obvious that it supports definitely the view that the reaction to irradiation is specific.

In successful irradiation of carcinomata the tumor is finally destroyed and its place is taken by fibrinous connective tissue. Even if the neoplasm is not entirely destroyed, the formation of connective tissue is marked and important, for it frequently encapsulates cancer cells. The fate of these encapsulated cells is unknown. There are many reasons for believing that the cancer cell requires an abundant blood-supply, of which these encapsulated cells are deprived; at worst, the cells are temporarily held in check. Furthermore, the formation of connective tissue probably, to an extent at least, acts as a barrier and temporarily checks the advance of the carcinoma.

Viewing the various histologic changes as a whole, Ewing believes that the more severe forms of radium reaction are not duplicated under any other condition, and indicate a specific and selective action of radium upon neoplastic tissue, an opinion that is shared by the authors.

Exhaustive histologic studies of irradiated malignant tumors have been made by Alter,²¹ Dominici, Rubens-Duval,²² Krönig,²³ Wickham,²⁴ Schmitz,^{25, 28} Ewing,²⁶ Bumm,²⁷ and many others.

The effect of irradiation upon experimentally produced malignant neoplasms in animals has been investigated by Wood and Prime,²⁹ Bashford, Murray and Bowen,³⁰ Apoland,³¹ Wassermann,³² Wedd and Russ,³³ Gudzent and Levy³⁴ and many others.

Whereas differences of opinion exist as to whether irradiation destroys malignant cells by a primary action upon the nucleus or upon the cytoplasm, all investigators agree that the neoplastic cell undergoes early solution, and that both nucleus and cell body are finally obliterated. Furthermore, it is generally accepted that the neoplastic tissue is replaced by fibrous connective tissue. Indeed some of the early observers were of the opinion that the primary action of radium was to produce fibrous tissue, and that, as a result of its contractility the neoplastic cells were squeezed out of existence. Encapsulation of neoplastic cells by this tissue is undoubtedly a factor in delaying the extension of irradiated malignant neoplasms, and is an argument against performing irradiation preliminary to operation.

It has been the experience of many investigators that when a cervical carcinoma in the third stage is subjected to irradiation, the tumor later may appear to be operable; the cervix becomes freely movable, hemorrhage and discharge cease, and the surgeon is tempted to perform a radical operation, more especially if he is inexperienced in radiotherapy. Under such circumstances rapid recurrence of the growth generally follows radical extirpation; this is often, in part at least, due to liberation, by operative trauma, of encapsulated cancer cells. Reference has previously been made to the probability of stimulating malignant cells by insufficient dosage of radium.

Wood and Prime³⁵ are of the opinion that this takes place. Ewing³⁶ refutes this statement, and the experiments of Hastings, MacCormac and Woodman³⁷ and Hertwig³⁸ appear to disprove this assertion. Hertwig showed that even extremely weak irradiation inhibited mitosis. The reports bearing upon this subject are, for the most part, inconclu-

sive, and the results of investigation, both for and against this theory, are frequently open to conclusions other than those drawn by their authors.

The rapid dissemination of a malignant tumor following irradiation has occasionally been observed. A number of theories have been advanced to explain this occurrence. The accepted fact that certain forms of malignant tumors are relatively insusceptible to irradiation combined with the trauma incident to the treatment may explain certain cases. Prolonged and especially ill-advised irradiation may develop an immunity to the rays, and the formation of cicatricial tissue may serve as a protective medium for the malignant cells.

Ewing³⁹ suggests that the obliterating arteritis that follows irradiation paralyzes the defensive reaction, and points to the fact that chronic infections often tend to become established in such lesions and to facilitate the extension of the malignant process. Finally, prolonged irradiation may injure the entire organism, especially the blood-forming function, so that the cancerous cachexia is added to the damage done by prolonged irradiation. It is well known that cachectic patients are unfit subjects for irradiation.

Despite the vast amount of work that has been done upon the subject of immunity to malignant disease, the authors believe that this problem is still an open one. In animals it appears that immunity against transplanted tumors can be produced. Unfortunately, immunity against autotransplantation is much more difficult to induce. Hence it will be seen that, as applied to metastasis and extension of growth beyond the operated or irradiated areas, the theory of immunity is of little practical clinical value.

In the vegetable kingdom it has been amply demon-

strated that weak doses of X-ray stimulate growth, and that certain grains that have been subjected to this treatment show more rapid growth and reach larger proportions than do the controls.

We feel that the subject of stimulation by irradiation and immunity is still unsettled, but that from a practical standpoint the fear of producing stimulation can be almost eliminated by the careful operator working in conjunction with a competent pathologist and physicist. There are three requirements for successful radiotherapy that have not, perhaps, been sufficiently emphasized. These are the services of a competent surgeon, a competent pathologist and a competent physicist. What would be adequate dosage for one tumor might be entirely inadequate for another, and the difference between neoplasms composed of embryonal tissue and those made up of adult type of cells constitutes a definite factor in the success or failure of radio-therapy. Thus unripe carcinomata yield quite readily to irradiation, whereas those of the squamous-cell or ripe type are relatively insusceptible to this mode of treatment. In cases of cervical carcinomata Ward and Farrar⁴⁰ employ a test dose of irradiation in order to ascertain the susceptibility of the tumor and of the surrounding tissue.

Biopsy is of value to the radiotherapist not only as a means of determining whether or not a given tumor is malignant, but also as a method by which the susceptibility of the neoplasm to irradiation can be ascertained. Even with all modern methods of diagnosis available, the recognition of malignant tumors is still difficult at times, and this difficulty is enhanced during the early stages of the disease. In the past the early recognition of malignancy was urged, especially by surgeons who are so frequently asked to operate upon hope-

lessly advanced cases, and who, in their follow-up work, are made familiar with the frequency of recurrence, even in cases that appeared moderately favorable at the time of operation.

The fundamental basis of all cancer propaganda has for many years stressed the necessity for early diagnosis, and this attitude will probably continue even if the cause of cancer is discovered in the near future. Certainly the early recognition of the disease is the most important point in any individual case, and has more definite bearing upon the ultimate prognosis than any other one factor. Early diagnosis is quite as important to the radiotherapist as to the surgeon. It must constantly be borne in mind that the earlier the diagnosis is made, the more favorable is the prognosis, and the more recent the lesion, the more difficult is it to recognize. Biopsy offers a safe, easy and almost certain method of diagnosis in all accessible tumors, and is employed extensively by nearly all specialists, who, as a class, see many more cases of malignant tumors than does the general practitioner, and who would, therefore, be more likely to recognize cancer in its early stages, which demonstrates that even the most experienced realize the difficulty often encountered in formulating an early diagnosis.

It is our belief, however, that the general practitioner is less prone to employ this easy method of diagnosis than is the specialist. For the radiologist or surgeon who employs radium or the X-ray in conjunction with surgical methods, biopsy is of the greatest help in determining the character of the tumor, and will often be the deciding point as to whether surgery or irradiation is the method to be employed.

Too often those inexperienced with the use of radium treat malignant tumors with irradiation, regardless of the histologic character of the neoplasms. As has been pointed

out previously, sufficient time has now elapsed to prove that various tumors respond differently to irradiation and the law of Bergonie and Tribondeau must be followed if the best results are to be secured. The part played by trauma in the dissemination of certain malignant tumor-cells is well known, and has been emphasized by Wood and his co-workers in the Crocker Institute. This and the rapid dissemination of certain tumor-cells following incomplete removal has led to doubt as to the advisability of employing biopsy in all cases.

Certainly in the class of new-growths generally encountered in gynecologic practice the use of biopsy is not attended with great danger and the disadvantages of delay far outweigh the slight hazards incumbent in this procedure. Ewing and others have declared themselves as advocates of biopsy—a declaration in which the authors emphatically concur.

Bloodgood favors the actual cautery as a means of performing excision, basing his choice on the theory that the cautery, as it cuts, seals up the avenue of possible dissemination. Ewing, on the other hand, advocates the use of a sharp knife, believing that the reaction and congestion incident to the cautery outweigh its advantages. The authors prefer a sharp knife, followed immediately by the cautery at a dull heat. The choice of either knife or cautery is purely theoretic and the important point to consider is the early recognition of the malignant character of the lesion under suspicion, and its susceptibility to irradiation.

Biopsy should be performed through the edge of the tumor, and, if possible, include a portion of the surrounding tissue. Necrotic parts of the tumor are not suitable for histologic purposes. One of the disadvantages of biopsy is that, as a rule, only a small bit of tissue is secured for histo-

logic examination, but a piece at least 2 cm. in diameter should, if possible, be excised. If a diagnosis of malignancy can be made from the examination of any given piece of tissue, it is generally possible for the experienced pathologist to prognosticate with a fair degree of accuracy, the susceptibility of the neoplasm to irradiation. It is most unusual to find one part of the tumor composed of undifferentiated cells and another area made up of an adult type of tissue.

Thus, for example, cervical carcinomata may be basal-celled or squamous-celled; these neoplasms being composed chiefly of the type of cell from which it takes its name; in other words, one part of the tumor is not basal-celled and another part squamous-celled.

Diagnostic curettage naturally falls under the category of biopsy. Sampson has decried this operation, asserting that transtubal dissemination of carcinoma cells is prone to occur. Both Sampson and the authors have demonstrated carcinoma cells in the Fallopian tubes following curettage. One of the authors has recorded the history of a case (Norris⁴¹) which they believe to have been one of transtubal dissemination of the cancer cells to the ovary.

The frequency of carcinoma of the body of the uterus associated with cancer of the ovaries is well recognized.

From what has been said it would seem possible, therefore, that curetting does occasionally play a part in the dissemination of fundal carcinoma. If the transtubal theory of the etiology of perforating cysts, as demonstrated by Sampson,⁴² is accepted, it is difficult to exclude the possibility of such transtubal migration of carcinoma cells following curettage. This operation itself breaks up the tumor and sets free many cancer cells within the uterine cavity; moreover the trauma incident to the operation is productive

of uterine contractures, which are likely to force out through the tube small gushes of blood containing cancer cells. If, in addition to this, if a uterine pack is used that prevents the free outflow of accumulated blood, the likelihood of dissemination appears even greater.

Intrauterine irrigation, or the piston-like action of the insertion of a radium-carrying rubber tube or other instrument at the completion of the curettage, may also be a factor in the dissemination of cancer cells. On the other hand, the early symptoms produced by carcinoma of the fundus, especially when it occurs prior to the menopause, are by no means characteristic, and although the Clark test, which consists of introducing under aseptic conditions, a uterine sound, is of distinct value, still the fact remains that a positive diagnosis can be arrived at only by performing a diagnostic curettage and making a histologic examination of the scrapings. Without curettage, either a number of early cases will be allowed to progress or many uteri not demanding hysterectomy will be removed. While, therefore, the authors recognize that curettage is not without its risks, these are far less serious than the results would be if the operation of diagnostic curettage were eliminated from the list of justifiable surgical procedures. Deaver and Reiman⁴³ have recommended a diagnostic abdominal hysterectomy—a procedure that the authors believe is entirely unjustifiable in most cases. With the aid of a competent pathologist, fundal carcinoma can be diagnosticated from curettings in practically 100 per cent. of cases.

Although many of the disadvantages of performing diagnostic curettage in cases of suspected fundal cancer, have here been enumerated, it is probable that many of these dangers are merely hypothetical. In a series of 57 cases of

fundal carcinoma, all of whom were ultimately subjected to hysterectomy, 40.9 per cent. survived three years who were submitted to a preliminary curettage and irradiation as against a salvage of 37.5 per cent. of cases that were treated by hysterectomy only or curettage immediately followed by hysterectomy.

It should be borne in mind that the cases upon which a diagnostic curettage was required were probably, as a group, in a somewhat earlier stage than those upon whom immediate hysterectomy was preformed. Nevertheless, the fact remains that better results were actually secured in the former group. These results may also have been influenced by the fact that in the group in which a diagnostic curettage was performed, intrauterine irradiation was employed almost routinely. With these facts in mind, the authors desire to state emphatically that they strongly advocate a diagnostic curettage in all cases of suspected fundal carcinoma in which a diagnosis cannot be arrived at with a reasonable degree of certainty by other methods. Following the diagnostic curettage, intrauterine irradiation is of distinct value. Owing to the histologic characteristics of fundal carcinoma, the dosage of irradiation should be at least twice that used in the case of an ordinary cervical cancer. Fundal carcinomata are more resistant to irradiation than are many of the cervical carcinomata, and require between 4000 to 8000 m. given intrauterinely. Care should be observed to secure thorough cervical dilatation in order to avoid the piston-like action that may develop during the introduction of the radium. Intrauterine irrigation and packing should be omitted.

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CHAPTER IV

MALIGNANT TUMORS OF THE EXTERNAL GENITALIA

CARCINOMA.—Among 1119 specimens of malignant new growths in the Gynecologic Laboratory of the University of Pennsylvania there are 30 carcinomata of the vulva. In the same laboratory there are 1049 carcinomata, so that, in our experience, cancer of the vulva represents 2.9 per cent. of all gynecologic carcinomata. Schöttlander and Kermänner¹ state that these tumors represent from 2 to 4 per cent. of all genital carcinomata.

Carcinoma of the vulva is a disease of advanced life, the average age of occurrence being about 60. Chronic irritation, pruritis, kraurosis, syphilis, elephantiasis, abscess, and especially leukoplakia appear to be etiologic factors in many cases. Certain forms of local infection generally precede the cancer. The majority of cases are of primary nature, although secondary lesions, the primary site being in the uterus or ovary, have frequently been observed. In the days when vaginal hysterectomy for carcinoma was more frequent, a number of instances were recorded in which implantation growths arose in the scars following paravaginal incisions. Amann² has reported the histories of a number of such cases. Clinically, the tumors appear to be of an ulcerative, papillary, or diffuse indurative form. The first of these is by far the most frequent. In the latter stages all varieties tend to become ulcerative, and as a result of the discharge, the surrounding parts soon become irritated.



FIG. 16.—Epidermoid carcinoma occurring in an aged woman. Practically the entire right labia was destroyed by an ulcerated new-growth which had been present for eleven months. The left labia was involved to a lesser extent. The inguinal glands on both sides were enlarged. Biopsy of the primary lesion showed a squamous-cell carcinoma.

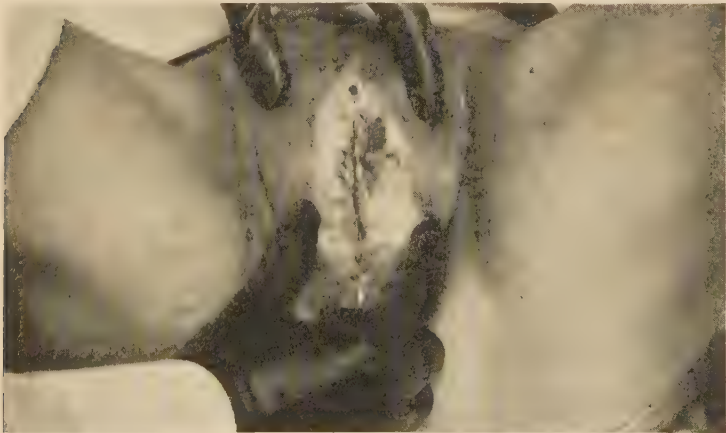


FIG. 17.—Same case as shown in Fig. 16 two months after treatment. This consisted in the implantation of emanation in the vulvar lesions, and X-ray to the inguinal glands. The patient was treated six months ago and at present shows no evidence of disease.

Implantation growths upon the opposite labia are frequent. Kehrer³ collected 35 such cases. Dittrich⁴ attributes the secondary growth to a lymphatic organ. Such lesions are common in advanced cases, but rare in the early stage. Metastasis to the inguinal glands occurs early. Dittrich⁵ found the inguinal glands involved in 50 per cent. of cases, and Rupprecht⁶ found them involved in his entire series. Adenitis may, however, be present without metastasis. Metastasis may also take place about the anus, in the abdominal wall, and in the thighs.

The common sites of development for the primary lesion are about the clitoris and upon the labia major. These areas are covered by modified skin, and the most frequent form of cancer in the epithelioma. An adenomatous variety may arise from Bartholin's gland. Falls⁷ collected 17 cases, of which about half were epitheliomata, the remainder being of the glandular type. Occasionally adenocarcinoma may arise from the urethra, clitoris, or sudorific glands. Primary urethral carcinomata are rare. In 1908 McMurtry⁸ collected 26 cases, and the authors have observed six. O'Neil⁹ collected 68 cases. Ruge¹⁰ has recorded the histories of two cases having their origin in the sweat-gland. Frankl¹¹ observed a case of carcinoma that had its origin in the hymen. The most common type of vulvar carcinoma, as stated, is the epidermoid.

The epitheliomatous type may further be divided into a typical squamous-cell variety, with prickly cells, pearl formation, and hornification, and a basal-cell variety, in which the cells are largely embryonal.

Syphilis, tuberculosis, chancroids, and granuloma inguinalæ sometimes produce clinical pictures closely simulating that of cancer. If any doubt exists, biopsy should be per-

formed. In fact, the microscopic examination should be employed in all cases, if only for verification: it is, at least to some extent, a guide as to the treatment. Many early cases of carcinoma of the vulva are mistaken for syphilitic manifestations if a positive Wassermann reaction is present.

Carcinoma of the vulva is an extremely malignant form of cancer, and recurrence is frequent, even following radical removal in apparently favorable cases. Metastasis to the inguinal glands occurs early, hence any form of treatment that is employed must take this fact into consideration. An explanation of the rapid course usually run by this disease is probably found in the rich lymphatic and vascular supply of this area and its exposure to minor traumas. Schulze, quoted by Ewing,¹² found, in 114 cases, 14 free from recurrence after five years.

Rupprecht¹³ considers the prognosis of the superficial forms comparatively favorable. Taussig¹⁴ reports that three of his nine cases treated by radical surgical measures remained well for five or more years. The same observer's careful review of the subject showed that 30 per cent. of cases treated by radical surgical procedures remained well. Zweifel¹⁵ and Schmitz¹⁶ have treated cases with satisfactory results.

Of the series recorded in the literature, many are small and others do not give the end-results. As a general rule, radical surgical excision, with the removal of the inguinal glands and the implantation of radium emanation in both the vulvar and inguinal wounds on both sides at the time of operation, followed as soon as healing has taken place by the application of the X-ray to all areas, offers the best hope of securing ultimate cure in the early cases. The basal-celled variety is most susceptible to the action of radium. One of

the authors has observed three advanced cases that were treated by radium emanation alone, complete local healing ensuing. A border-line case, as far as surgery was concerned, was treated in a similar manner, radium packs and X-rays over the inguinal region being also employed. This tumor was of the basal-celled type. The enlarged inguinal glands disappeared and complete local healing occurred.

For the advanced cases, gold encased emanation constitutes the treatment of choice. By their use a palliative effect can generally be secured, life prolonged and rendered more comfortable, and in a small proportion of cases a permanent cure may be obtained. Recently, one of the authors has treated a small series of cases by electro-desiccation combined with radium emanation with apparently good results. This form of treatment is worthy of a further trial and possesses the advantage that it is suitable for advanced cases. By this method and if necessary dividing the treatments over two or more sittings excellent local healings have been secured.

In the writers' experience, the squamous-cell type is most resistant to radium, the adenocarcinoma standing between this and the unripe cell variety. The authors are not aware of any large series of cases of vulvar carcinoma that have been studied from the histologic standpoint, and that have been treated by radium or in combination with the X-ray from which a comparison of end-results can be made. Certain forms of vulvar carcinomata, notably the basal-celled neoplasms, appear quite susceptible to irradiation, whereas others continue their malignant course even after full dosages of either radium or the X-ray have been used.

Moreover, the primary growth is generally more susceptible to treatment than are the metastasis. Despite the fact that the inguinal glands are superficial and easily accessible

for irradiation purposes, metastasis in these often continues to advance under dosages that are at least distinctly palliative to the vulvar neoplasm. Bailey and Bagg¹⁷ have treated ten cases of vulvar cancer with radium; in some the inguinal glands were excised. They employ "seeds" of 0.5 mc. value, using one tube to each square cm. of area. They also

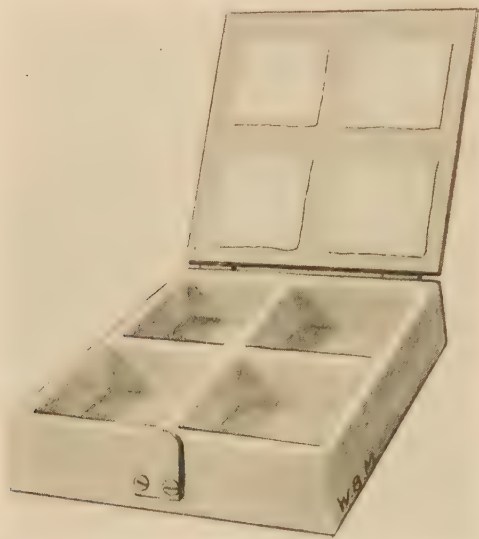


FIG. 18.—Container for radium emanation.

implant the radium seeds about the edges of the growth. Three weeks later they examine these cases and generally give a second treatment. The inguinal region is treated with 3000 mc. hrs. at 4 cm. with lead "blocks." Six weeks later, if there is palpable enlargement, the glands are excised. After removal of the glands unfiltered tubes of 0.3 to 0.5 mc. each are laid 1 cm. apart in the wound, and if possible, they are implanted also into the stump of the lymphatic chain. Excellent results were obtained by this method.

Radium irradiation is especially valuable in urethral carcinoma, which, owing to its location, frequently precludes radical removal by surgical measures. Schmitz,¹⁸ Shaw¹⁹ and others have reported good results following the treatment.

SARCOMA OF THE VULVA is a rare tumor, but one example of this neoplasm being among the specimens in the Gynecological Laboratory of the University of Pennsylvania. It occurs most frequently between the ages of 40 and 50, although cases in the extremes of life have been recorded. The tumor generally begins as a firm, localized nodule, that grows rapidly according to the type of cells of which it is composed. It ultimately breaks down, leaving a ragged, hard ulcer. Metastasis occurs early.

Various histologic classifications have been suggested. That which classifies them as round-celled, mixed-celled and spindle-celled is perhaps the most satisfactory. According to Frank,²⁰ who has collected the literature on this subject, the proportion of cures varies from 7 per cent. (Kehrer) to 25 per cent. (Jacoby²¹), the average being about 14 per cent. Veit²² has recorded the history of a case of sarcoma that originated in Bartholin's gland. The tumor was non-pigmented. This observer found but two similar cases in the literature, one by Hofmeier and another by Blumm, and his study shows further that there are about 50 cases of non-pigmented sarcomata of the vulva recorded.

Veit and Frank²³ believe that the majority of pigmented sarcomata recorded in the literature are melanomata. Ewing²⁴ admits his inability to reach a conclusion on this point. According to the last-named investigator, melanoma is a pigmentiferous tumor arising from a specific mesoplastic cell, the chromatophore, and possibly also from epithelial cells that have been modified by pigment production. In the skin

its origin is connected with a congenital abnormality consisting of overgrowth and pigmentation of epidermis, and often of the cutaneous glands, occasionally with angiomatous processes and especially characterized by the presence of many peculiar abnormal cells in the derma, forming a lesion known as congenital nevus. In many cases this tumor terminates in an extremely malignant new-growth, with rapid proliferation of its cells and metastasis. The authors have seen such a case, recurrence taking place three times at intervals of a year or two. At each excision the tumor was small and did not appear particularly malignant, nor were there evidences of metastasis. The growth appeared upon the outer surface of the labia majora, recurred in each instance in the cicatrix, and was removed when about 1 or 1.5 cm. in diameter. This tumor was suggestive of a connective-tissue origin. This patient finally died from a recurrence seven years after the onset of the disease. Ferguson²⁵ and Lockhart²⁶ have recorded similar cases.

Melanoma generally develops upon the outer surface of the labia or in the region of the clitoris, and appears as a pigmented tumor. At times they are pedunculated, but more often they are sessile. Neoplasms that grow rapidly tend to ulcerate and give rise to early metastasis. For literature on these growths see Rothschild,²⁷ Meyer²⁸ and Fisher.²⁹ The treatment for sarcoma and melanoma is the same as that which is indicated for carcinoma.

CONDYLOMATA ACUMINATA. —Condylomata acuminata, verruca acuminata, or venereal warts, are a frequent accompaniment of vulvitis, and are found most often among the uncleanly. They are particularly likely to appear if pregnancy should take place. These tumors occur more frequently and attain greater dimensions in women than in men, owing

to the fact that in the former the gonorrheal discharges are constantly brought in contact with the vulva, perineum, and adjacent skin surfaces. The tumors may surround the anus, and on separating them, a fistula in ano is not infrequently found. Children are by no means immune, and infants and young girls suffering from vulvovaginitis are frequently attacked. Smith³⁰ has reported the occurrence of venereal warts of gonorrheal origin in an infant nineteen months old.

The vegetations vary in size from extremely small growths to tumors the size of a man's fist. They may occur as discrete excrescences, or they may coalesce, forming large, cauliflower-like neoplasms. The confluent tumors usually originate from a broad sessile base, whereas the discrete warts are not infrequently pedunculated. These outgrowths, except when they are modified by local conditions, are similar in color to the surrounding skin. Not infrequently, as a result of being continuously bathed in an irritating discharge the warts become reddened or purplish in color and very vascular. Their surfaces may be macerated. They may be present on the vulva or contiguous skin surface, or, more rarely, may extend into the vagina. The symptoms arising from the presence of condylomata acuminata are similar to those of chronic vulvitis. The exudate is usually thin, offensive, and highly irritating. The more vascular the warts and the thinner their epithelial covering, the more profuse is the discharge. The diagnosis is, as a rule, not difficult. The possibility however, of syphilis being the etiologic factor should always be considered before treatment is instituted. In general, gonorrheal vegetations may be distinguished from syphilitic condylomata by their smaller size and pointed appearance, the growths due to specific disease being, as a rule, flat and broad. In neglected cases too much weight

should not be placed upon the appearance of the growth, but other symptoms and evidences of syphilis should be looked for. It should also be remembered in this connection that both diseases may coexist.

Condylomata acuminata probably are largely toxic in origin. The author has never been able to demonstrate the presence of gonococci in these tumors, although repeated efforts have been made. The organisms are frequently found upon the surface and in the crypts of the tumors. Similar results have been obtained by a number of other investigators. Streptococci and staphylococci have, however, been observed.

TREATMENT.—As a general rule, irradiation is not the method of choice. As the lesions occur during the child bearing period especial care must be observed not to destroy the menstrual function. Venereal warts which are especially suitable for irradiation are the pedunculated tumors. Where great masses of the warts are present methods other than irradiation should be employed. Irradiation may well be utilized during the last two or three weeks of pregnancy in selected cases and is less likely to result in a premature labor than are the ordinarily employed surgical procedures. Radium seeds are especially applicable in the treatment of these lesions. Cleanliness is essential and every effort should be made to check the discharge coming from areas higher in the genital tract.

CASE OF VENEREAL WARTS TREATED BY IRRADIATION.—The patient was a white female, 20 years of age, single; occupation—child's nurse.

FAMILY HISTORY.—Father and mother are living and well; no history of tuberculosis or malignancy. One sister and two brothers living and well.

PAST HISTORY.—As a child, the patient had chicken pox and measles and occasional attacks of tonsillitis. Otherwise,

history is negative and health has always been good. Menstruation was established at fourteen, 28-day interval, lasting four days, normal in character and amount. Last period, May 20, 1924.

PRESENT ILLNESS.—Patient admits a Neisserian infection in March, 1924. Shortly after exposure to infection the patient noticed a vaginal discharge, and symptoms suggesting a urethritis developed. The vaginal discharge increased in amount and became mucopurulent. Chafing of the vulva and thighs became increasingly severe as the mucopurulent vaginal discharge increased. Patient became alarmed and consulted physician in April who gave her local treatments three times a week, the character of which is not known. No relief was obtained. About the middle of April she noticed small wart-like growths on the external genitalia which subsequently grew rapidly.

On admission to the Radiologic Department of the Philadelphia General Hospital the pelvic examination showed the vulva reddened and inflamed. A profuse thick, yellow discharge was present. The vulva from the mons to the anal orifice was studded by numerous wart-like growths, some separate and some in conglomerate masses. A number of these lesions have extended to the inner surfaces of the thighs. The smallest are pin-point in size, the largest have a diameter of one centimetre. Otherwise, the anatomical formation of the vulva was normal. The vagina was normal. A well-marked subacute cervicitis was present. The cervix was freely movable; the fundus was in anteposition and normal in size, shape and mobility. The tubes and ovaries were normal. Physical examination showed a medium-sized young adult, with no appreciable deformities; heart and lungs were normal. Abdominal examination was negative.

LABORATORY REPORTS.—The urine was normal and the

Wassermann test was negative. The cervical smear showed numerous intracellular organisms morphologically and tinc-torially resembling the gonococcus. A biopsy taken from the vulvar lesions showed the usual histologic structure of condylomata acuminata.

TREATMENT. Radium was applied in silver tubes to three different areas over the labia, giving a total dosage of 511 mc. hours over area one; 469 mc. hours over area two; 257 mc. hours over area three.

RESULT.—An excellent result was obtained. Two months after treatment there was no evidence of recurrence and the skin was smooth and healthy. The menstrual function was not disturbed.

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CHAPTER V

MALIGNANT TUMORS OF THE VAGINA

Primary malignant tumors of the vagina are rare, the secondary neoplasms, due to implantation, being more common. Extension to the vagina from adjacent new-growths is of frequent occurrence. Cullen¹ records the history of a case which he believed due to retrograde metastatic embolism from the uterus. Carcinoma of the vagina is the most frequent malignant tumor occurring in this region.

Primary carcinoma is commoner in multiparas. According to Schwarz,² primary carcinoma of the vagina constitutes 0.24 per cent. and according to Gurlt,³ 0.19 per cent. of carcinomata occurring in the female genital tract. At the Laboratory of Gynecological Pathology at the University of Pennsylvania there are 11 specimens among 1049 genital carcinomata. The average age is from 35 to 55, although extremes have been observed. For literature on this subject, see Ward.⁴

Chronic irritation appears to play a definite rôle in the etiology, and leukoplakia frequently precedes the cancer. The authors have observed one advanced case that occurred in a woman who had worn a large glass pessary for twenty years without removing it, the surrounding structures having become eroded. Maly,⁵ Schlund⁶ and others have recorded similar cases. A few instances have been recorded in conjunction with prolapse (V. Schmidt and Fleck⁷). It would seem that prolapse might constitute a marked predisposing factor to the development of carcinoma, but such is not the case. The thickened or "washerwoman's skin"

serves as a protective agent against infection and, as a result, chronic irritation is rarely present. Even the decubitus ulcers which occasionally occur in these cases are always indolent and inactive. The authors have never seen a carcinoma that had its origin in a decubitus ulcer.

In the great majority of cases vaginal carcinoma has its origin upon the posterior vaginal wall, often just below the cervix—in that area on which a heavy lacerated cervix is prone to rest, and which is naturally the point most likely to be subjected to maceration and irritation from cervical discharges. The tumor is either ulcerative or papillary in type. Ewing describes a diffuse infiltrative form, often annular in type, a variety not observed by the authors. Vaginal carcinoma is rarely seen in the first stage. Metastasis takes place early. The lymphatics of the upper third of the vagina drain into the iliopelvic chain and join those of the cervix. Metastasis occurs from the middle third to the lowest nodes of the iliopelvic and hypogastric groups, and from the lower third to the inguinal region. Owing to the thinness of the vaginal walls, fixation and extension to the surrounding parts occur early. The greater frequency of carcinoma on the posterior vaginal wall together with the lymphatic drainage accounts for the frequency with which involvement of the rectum takes place. Extension to the cervix and base of the broad ligament is also common. In many instances it is impossible to determine whether the cancer originated in the cervix or in the vagina, the former being the more usual primary site.

Histologically, vaginal carcinomata may be epidermoid or glandular. As the vagina contains few glands and scanty glandular tissues, the former variety is by far the more frequent. Among the epidermoid cancers, prickly cells and

true cornification are occasionally encountered. As a rule, however, the tumor is made up of masses of more or less undifferentiated cells, frequently with little stroma and of a type that would appear moderately susceptible to irradiation.

TREATMENT.—Carcinoma of the vagina generally arises in the upper third and on the posterior wall, probably the most difficult parts of the genital tract to reach by radical surgical measures. As the disease is not a very common one, there are but few reports of large series in the literature and even fewer that deal with end-results. This applies to cases submitted to operation or to irradiation. When the tumor is discovered in the early stage of growth and is accessible to wide excision, this operation should be performed, emanation being implanted at the time of the procedure and postoperative irradiation by means of deep X-ray therapy instituted.

If the primary lesion is situated in the lower portion of the vagina, the inguinal glands should be excised and emanations implanted at the time of operation. The other areas of probable metastasis should be subjected to deep X-ray irradiation as a postoperative precaution. The patient should be examined at intervals of three weeks and local recurrences should be treated with gold tubes. Unfortunately, most of the cases of vaginal carcinoma are not seen early, and in these radium therapy, alone or in combination with the X-rays, offers the most satisfactory form of treatment. Bailey and Bagg⁸ and Philipp and Gornick⁹ state that carcinoma of the vagina has an unfavorable prognosis. Of 53 cases treated with radium only 13.2 per cent. survived the five-year period. Only ten of these cases were in an operable stage at the time of irradiation.

Stacy¹⁰ records the histories of 21 cases, 14 of which had

a follow-up for varying periods. Seven were living at the time of this report, the longest period being four years since operation. The seven who died survived for periods varying from five months to four years.

The histologic types of vaginal carcinoma closely resemble those of cervical cancer, and following irradiation similar results may be expected, provided it is possible to subject the neoplasm to the same irradiation dosage. Unfortunately, this is not always feasible. Owing to its anatomic location the cervix is particularly favorable for irradiation. Not so with vaginal tumors; here the danger of fistula is always present, and the utmost care is necessary to avoid the occurrence of this unpleasant complication. However, the likelihood of the production of fistula is just as prone to follow surgical removal of the neoplasm. Keene¹¹ observed this complication three times among 17 cases of vaginal and vulvar carcinoma treated in the Gynecologic Department of the University Hospital.

In considering the incidence of fistula following irradiation, it must be remembered that a certain proportion of them are due to the disease itself, and that if the cases were allowed to proceed untreated, many more fistulæ would probably develop than in the treated cases. In hopeless cases the irradiation treatment has no superior as a palliative measure and even in those that terminate fatally life may generally be prolonged and rendered less uncomfortable. Far-advanced cases or those in which treatment is impossible without almost certainly producing a fistula are better without irradiation, but may sometimes be improved by carefully administered X-ray therapy. The same is true of those cases in whom fistulæ have already developed.

SARCOMA.—Primary sarcoma of the vagina is a rare neo-

plasm. In 1911 McFarland¹² collected 68 cases. Sarcoma has been described as occurring at various points in the vagina. The growths may be nodular, sessile or pedunculated. Diffuse, obstructing types have also been observed. Necrosis at the apex of the tumor often occurs early, resulting in a broken-down, sloughing mass. According to Bland,¹³ metastasis occurs late, but the time of occurrence probably varies with the histologic type of the tumor.

The ultimate prognosis is unfavorable (Spiegelberg¹⁴). Of the varieties that have been described, the most frequent is the spindle-celled type, although round-celled, giant-celled, spindle-celled, alveolar, myxomatous and telangiectatic forms have been encountered. For the literature on the subject see Jellett and Earl,¹⁵ Graefe¹⁶ and Dellepione.¹⁷

Secondary vaginal sarcomata have been observed. The primary growth may have its origin in the uterus or about the external urinary meatus or vulva; for the literature on these types see Hofmaki¹⁸ and Kaufmann.¹⁹

The treatment consists of a combination of radical excision and emanation implantation, followed by post-operative irradiation by means of deep X-ray. Radium application or X-ray therapy probably offers the best hope of effecting permanent cure in the early cases. If the tumor is situated near the orifice of the vagina, excision of the inguinal glands on both sides, and irradiation of this area with emanation, followed three or four weeks later by deep X-ray therapy, are indicated.

MIXED TUMORS AND TERATOMATA.—These neoplasms are often classified as sarcomata (*sarcoma botryoides*). They are rare neoplasms, and occur almost exclusively in children; apparently they are congenital. The tumor may occur in infancy, and when first observed is a soft, vascular, semi-

translucent, sometimes pedunculated neoplasm, generally springing from the anterior vaginal wall. In one or two instances the tumor was not detected until the child was between 12 and 15 years of age (Ahfeld²⁰). This may be explained by the existence of a congenital anlage. The neoplasm may remain quiescent for varying periods, but, as has been stated, it generally develops early. The neoplasm grows rapidly, becomes lobulated, new polypoid masses develop, the vagina becomes filled and distended by the new-growth, which projects beyond the vulvar outlet; the vaginal walls become infiltrated, and intravesical development frequently takes place.

Necrosis is prone to occur. Pyometra, pyonephrosis or general peritonitis may result. Regional and widespread metastases develop and recurrence and death generally follow all forms of surgical intervention. Volkman²¹ has recorded a permanent cure. All tumors, especially the vascular polypi, occurring in infants or young children and springing from the vagina, should be regarded with suspicion and immediately subjected to histologic examination.

Histologically, the tumor consists of mesodermal elements, spindle cells, myxomatous tissue, striped and unstriped muscle tissue, cartilage, round cells, epithelial cells, and various other constituents. The spindle-celled type, in which the cells are arranged in a sarcomatous-like structure, is the most common. Myxomatous tissue is, as a rule, present. The tumors are generally extremely cellular. Edema, especially of the central portions, may be marked. For literature on these neoplasms see Frank,²² Wilms,²³ Veit,²⁴ Soltmann,²⁵ Pick²⁶ and Hurden.²⁷

The authors have had no experience with the treatment of these tumors. On account of their embryonal character,

these neoplasms would appear especially suitable for irradiation, but, owing to their extreme malignancy and early and probably frequent blood-borne metastasis, the prognosis is at all times unfavorable. Israel²⁸ excised the entire vagina and uterus by the sacral route in a nine-month-old infant, but a recurrence rapidly developed.

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CHAPTER VI

MALIGNANT TUMORS OF THE CERVIX UTERI

CARCINOMA.—This is the most frequent malignant tumor encountered in gynecologic practice. Among 11,416 specimens in the laboratory of gynecologic pathology at the University of Pennsylvania 530 cases of cervical cancer have been encountered. So that cervical cancer constituted 4.9 per cent. of all cancers of the genital tract. At the Philadelphia General Hospital the proportion of cervical cancer is even higher. Camperman¹ found that cervical cancer constituted four per cent. of all gynecologic practice.

Cervical carcinoma occurs in one of three clinical types, (a) ulcerative, (b) papillary, and (c) interstitial. All varieties become ulcerative in the late stages. A detailed description of these well-known lesions is not required. The ulcerative is the most frequent, and in comparison with the others the interstitial is infrequent, which is fortunate as it is often advanced before reaching the surface and producing symptoms. Ruge and Veit attempted to classify the tumor according to their point of origin. In many cases this is impossible and the classification is therefore unsatisfactory. Histologically the tumor may be epidermoid or glandular. The former may be further divided into basal-celled, transitional-celled, and squamous-celled cancer types. The basal-celled tumor contains little stroma and presents large cords or islands of rapidly proliferating epithelium.

The cell nests are the most prominent feature, the stroma is scanty and vascular. The centres of the epithelial islands frequently undergo necrosis, become filled with pus and form

channels leading to the surface. The cancer cells are relatively large, relatively regular in size and rounded or polyhedral. No trace of pearl formation is present. In the transitional-celled type, the majority of the cancer cells are distinctly transitional in character. Occasionally a few giant cells are present. Mitotic figures are very numerous. Isolated cancer cells are frequently present in lymph spaces, especially toward the periphery of the new-growth. In the squamous-celled type the stroma is a more prominent feature and typical prickle cells are present. Pearl formation is often observed. As a differentiating point the prickle cell is of more value than the pearl and indeed it is probable that the formation of pearls is merely incidental. The cancer cells as a whole are more differentiated than in the former variety. Giant cells are of frequent occurrence. Mitosis, although frequent, is a less prominent feature than in the basal-celled form. Multiple mitosis, hyperchromatosis and karyorrhexis may be present. Occasionally, a fourth type of epidermal cervical carcinoma is encountered in which there is a mixture of the preceding types.

Adenocarcinoma of the cervix is not infrequent and arises from the mucosa. This does not exclude the origin of this tumor from the exposed vaginal portion of the cervix as carcinoma generally arises in lacerated cervixes and the tumor frequently springs from the everted portion of the mucosa. The lesion presents the usual characteristics of an adenocarcinoma. The epithelium is generally rather low columnar, and only in rare instances retains the high goblet-like form from which it springs.

ADENO-ACANTHOMA OR ADENOCANCROIDS.—Occasionally tumors which appear to be combinations of the squamous and adenomatous type are met with. These are not of multi-

FIG. 19.—Epidermoid carcinoma of the cervix, stage (I).



centric origin, except perhaps in rare instances. Metaplasia of the cylindrical cells into squamous type is of frequent occurrence in cervical mucosa exposed to bacteriologic or chemical irritation. Hitschman believes that this metaplasia may be complete and produce prickle cells and keratohyalin.

Although the histologic pictures in any given tumor often vary in different portions due to age, degenerative processes

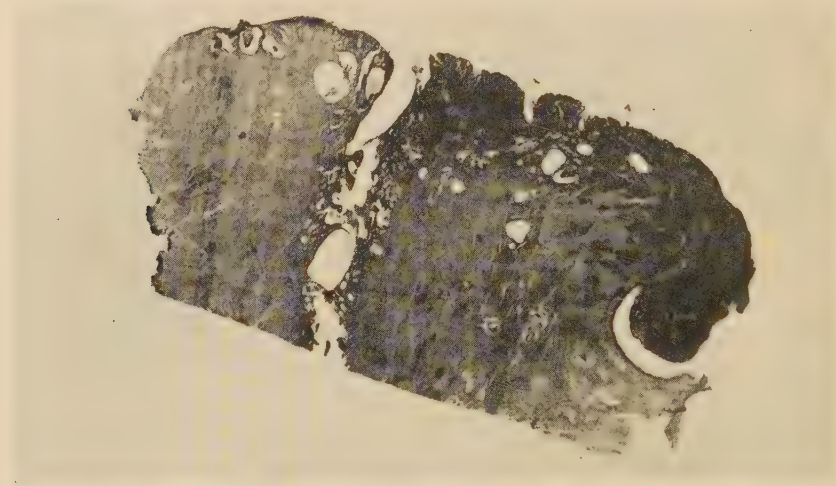


FIG. 20.—Adenocarcinoma of the anterior cervical lip. Trachelectomy performed with the cautery followed by irradiation. Patient well five years later.

and the anatomic site invaded, the same type of tumor is present throughout. In other words, the pearl-forming tumor is always of the squamous type, an adenocarcinoma always of the glandular type. An exception to this may be found in tumors of multicentric origin, but this is of extremely rare occurrence. This is an important point and bears on the value of biopsy.

It appears well proven that certain types are more malignant than others and that certain tumors are more suscep-



Fig. 21.—Adenocarcinoma of the cervical canal. An area of carcinoma can be seen in the posterior wall of the cervix. This patient gave a typical history of carcinoma. Palpation and inspection were negative and it was not until a sound was introduced into the cervical canal that the extent of the disease was recognized.

tible to irradiation than others. Martzloff² in his careful study of 387 carcinomata found that he was able to divide the tumors into three groups according to the predominant cancer cells present. These were the transitional, spinal cell and fat spindle types. His studies, based upon a check-up on end-results, showed the following types in their order of malignancy: the fat *spindle*-celled type was the most malignant, next the *transitional*, then the *adenocarcinoma* and the *spinal* or prickle cell types the least malignant. He found involvement of the broad ligament in the first six months from the onset of the symptoms in all groups except the last mentioned.

This work has been largely verified by one of the authors who is in general accord with Martzloff's conclusions as above quoted except that the fat spindle and transitional types in some specimens appear to overlap and be difficult to differentiate, and that these two types, even when typical, appeared of about equal malignancy. As a general rule the greater proportion of undifferentiated cells present and the greater percentage of mitosis observed, taken in conjunction with the tendency of the cancer cells to break through their basement membrane, the more rapid is the growth of the neoplasm and the greater is its malignancy. Our own investigation with cervical carcinomata confirms the previously quoted law of Bergonie and Tribondeau, that the more embryonal the cell the greater is its susceptibility to irradiation. In an analysis of our own cases with this end in view Kimbrough and one of the authors³ found that the tumors containing a predominance of embryonal cells responded to irradiation as far as local healing was concerned in 76 per cent. of cases, whereas in those tumors containing a large proportion of a more mature type of cell showed local healing



FIG. 22.—Carcinoma of the cervix stage (ii). A small myoma and hyperplasia of the endometrium are also present.

following irradiation in only 51 per cent. of cases. As far as end-results were concerned there was little difference between the different groups, a fact which may probably be explained by the greater malignancy and earlier metastases of the former counterbalancing its greater susceptibility to the effects of irradiation.

Pomeroy and Strauss,⁴ after the study of 75 cases, came to a somewhat similar conclusion. They found that nearly three-quarters of the cases that responded well to radium irradiation were of the transitional-cell type. This brings up the question of whether, other conditions being equal, the dosage of irradiation should not be governed by the type of cell comprising the bulk of the tumor. Schmitz⁵ states that basal-cell carcinomata of the cervix respond rapidly to a 100 per cent. E. S. D. with local healing and negative microscopic findings, but that the adenocarcinomata and squamous-cell cancers require 150–175 per cent. E. S. D. to secure similar results. The latter dosage causes scarrings and second degree burns of the normal epithelium.

Schmitz's conclusions are based upon the study of 100 cases. Schmitz, Hueper and Arnold⁶ in a recent study in a large measure confirm the previous findings of the senior author. They have given a numerical value to the various factors, the sum representing the histological malignancy index. They state that the relation of the cell type to the histological malignancy index is definite. The unripe cell type is always associated with a high malignancy index. Lahm⁷ and Roussy⁸ believe the microscopic examination is of definite value as a prognostic aid.

We believe the transitional-cell type to be the most frequent, the most malignant, the least favorable for operation and the most susceptible to irradiation. The probable expla-

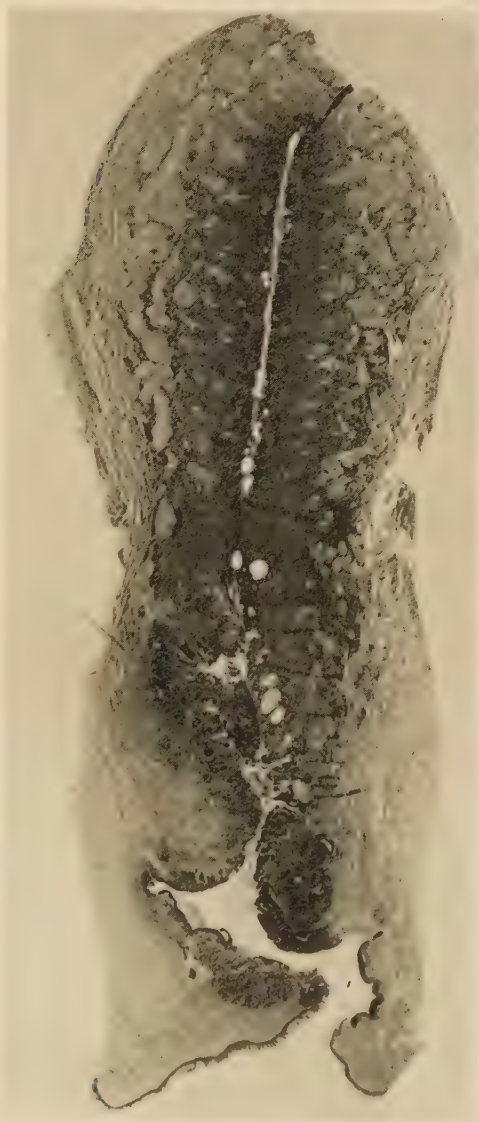


Fig. 28.—Adenocarcinoma originating in the cervical canal with extension to the vagina, stage (iii).

nation of the reason that a greater proportion of the unripe tumors are not cured by irradiation lies in the fact that they, being more malignant, probably extend beyond the cervix earlier and give earlier metastasis than do the other forms, and that by our present methods some cancer cells extending from or part of the primary tumor are insufficiently irradiated and the fact that the metastases are less susceptible to irradiation than are the cells of the primary growth. A very satisfactory classification of cervical tumors is that employed by Fluhmann⁹ which consists of grouping the cases under three headings: the ripe, the midripe and unripe according to the predominant type of cell present. This author believes that the immature types do better with radium. He further states that the presence of large numbers of eosinophiles in the tumor may be a favorable prognostic sign after irradiation.

SYMPTOMS.—Hemorrhage and discharge are the only symptoms of value in the diagnosis of early cervical carcinoma. Anemia, cachexia, loss of weight and pain practically always indicate an advanced stage. Pain may be due to cellulitis alone, but when fixation or thickening of the broad ligament is present extension beyond the cervix has generally occurred.

There is no need in this work to review the symptomatology of cervical carcinoma in detail. The hemorrhage is intermenstrual, of the "spotting" type, generally small in amount in the early stages, progressive and as the tumor is friable and vascular it tends to follow trauma; it is painless and bright in color. It is probable that cancer in no way influences menstruation in the average case. Occasionally apparent prolongation of the normal period may be produced by the occurrence of a hemorrhage, either just preceding or

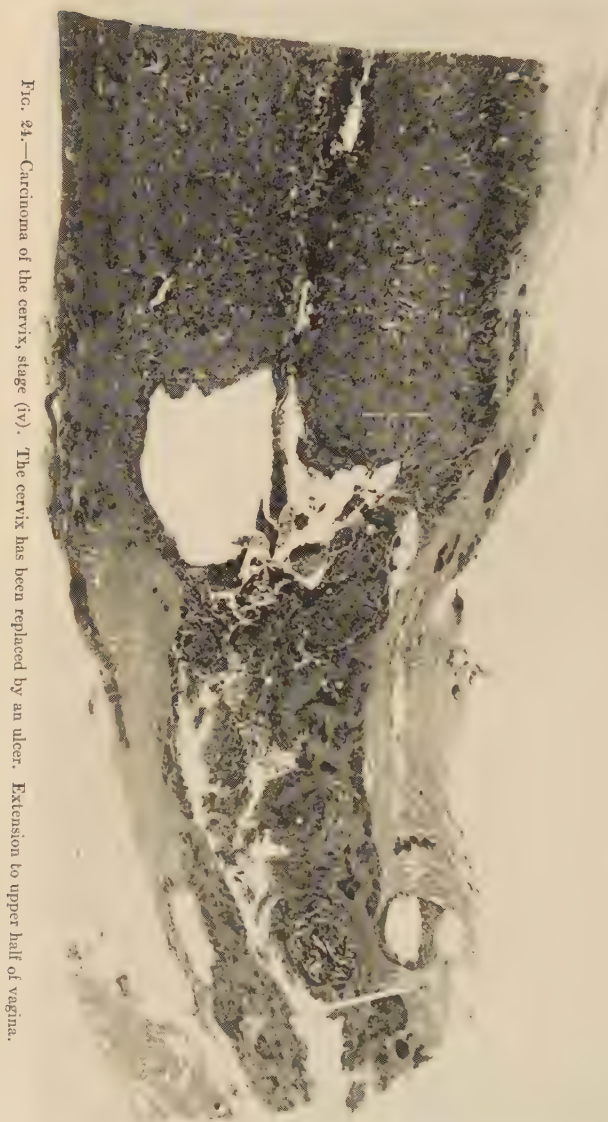


FIG. 24.—Carcinoma of the cervix, stage (iv). The cervix has been replaced by an ulcer. Extension to upper half of vagina.

following the monthly period. Occasionally, especially in the interstitial form, the first symptom may be a massive hemorrhage due to the erosion into a blood-vessel. Metastasis or accompanying inflammatory lesions of the ovary may occasionally cause menorrhagia. This, however, is uncommon.

The development of cancer is infrequent in a normal cervix, the organ usually being the seat of a laceration and infection; these conditions in themselves produce leukorrhea, and the only diagnostic value of discharge is its development when it has previously been absent, or it increases in amount or changes in character when it has formerly been present.

The discharge due to cancer is at first scant, thin and slightly malodorous, and is rarely noticed; later it becomes thick, dark, irritating, profuse, and distinctly offensive. By the time the discharge has become pronounced, irregular hemorrhages have usually been present for some time. This is in accord with the histology of the lesion. During the early development of the cancer the discharge is due to hypersecretion of the adjacent glandular structure, augmented by the secretion from the tumor itself. As soon as necrosis of the tumor begins this detritus is added to the discharge. As a result of the irritation, the nearby glands become more active. It is rare for the tumor to advance to the stage of necrosis prior to the development of small hemorrhages. As a diagnostic symptom we would value hemorrhage as ninety points and discharge as ten points. Schmitz¹⁰ among 406 cases of cervical carcinoma found hemorrhage the most prominent symptom in 61.5 per cent., and discharge in 14.7 per cent. These, however, were not all early cases.

Early cervical cancers are rarely observed. It is probable



FIG. 25.—Epidermoid carcinoma of the cervix, stage (iii). The patient was unusually stout and the uterus in acute retroflexion. In an effort to locate the cervical canal a sound was passed through the carcinomatous anterior lip, under the bladder and through the vesical peritoneum resulting in peritonitis and death. A small pyometra is present. This is the only case of this kind of which we have record and illustrates a rare danger of irradiation. The necrotic tract left by the sound and a part of the bladder are well shown.

that the disease is often much more insidious than most text-books would indicate. It is the unfortunate experience of every surgeon to not infrequently encounter advanced cases in which the closest inquiry fails to reveal symptoms having been present for any considerable length of time.



Fig. 26. Fimbria from specimen shown in Figure 24. Nearly every lymphatic space is invaded by carcinoma cells. The endometrium is practically normal. Postmortem specimen from P. G. H.

During the early stage of the interstitial variety no symptoms are present except a slight nodule, which is likely to be discovered only by accident. This is, however, a relatively infrequent form and it is probable that other types, especially those developing within the canal, frequently become advanced before any subjective symptoms develop.

At best, the symptomatology of early cervical cancer is mild and painless, and it is due to this fact and that the disease generally develops at the time of the menopause when irregularities are expected by the laity, that the lesion is so rarely observed in the early stage.

In a series of 361 cases from the Radiologic Department of the Philadelphia General Hospital, the average duration of

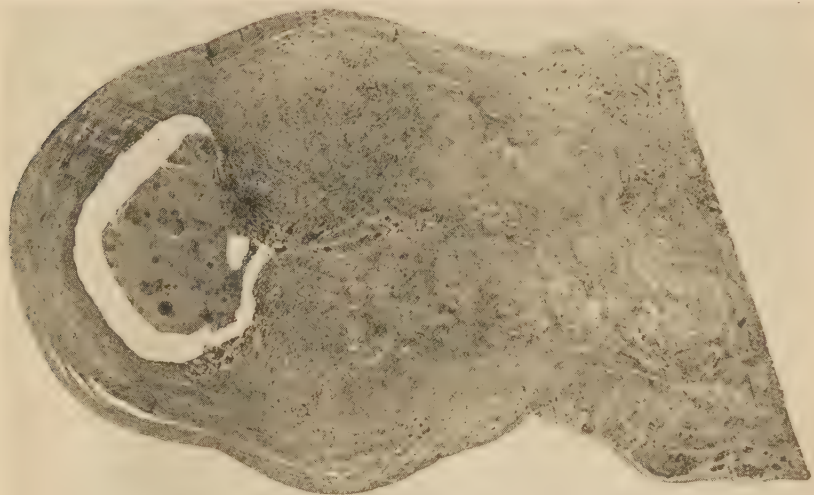


FIG. 27.—An epidermoid cervical carcinoma has invaded upwards until little of the normal myometrium remains. A small pyometria is present.

symptoms prior to seeking medical advice, was three to four months. It is obviously unjust to blame the general practitioner for the advanced stage in which many cases are seen by the consultant. With our present knowledge of cancer, anti-cancer campaigns would do well to stress the ominousness of irregular, painless bleeding at or about the menopause especially that which follows trauma or which is post-menopausal, as well as the advantages of regular periodic pelvic examination during the cancer age. Prophylaxis of

cervical laceration and especially in their repair is of the utmost importance.

Of late years the unfortunate term "precancerous" has crept into the literature pertaining to this subject. This is a dangerous and inaccurate term. Lesions are either cancer or

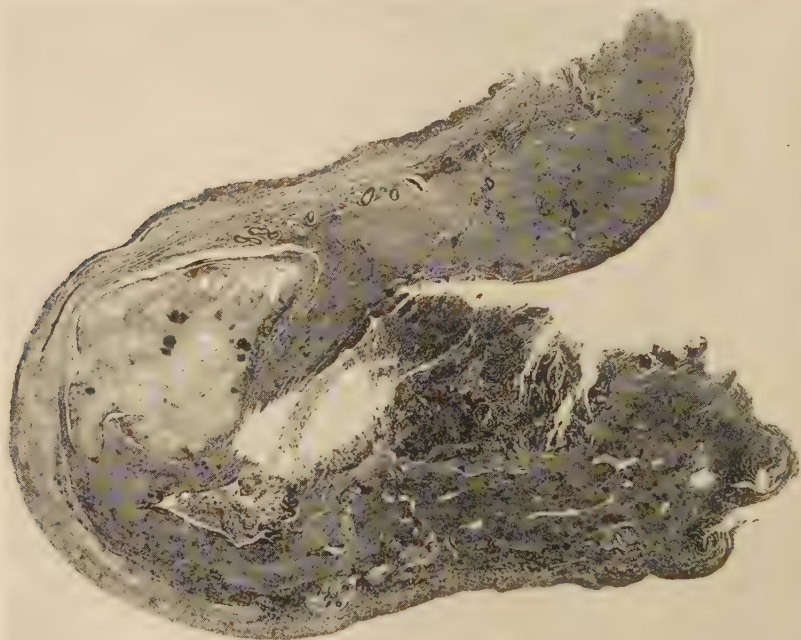


FIG. 28.—Adenocarcinoma of the cervico-uterine junction. Myoma of the uterus and hyperplasia of the endometrium.

not cancer. At the stage when patients generally seek medical aid the diagnosis of cervical cancer can nearly always be made by clinical methods by one experienced in this work, and the earliest stage of cancer can be positively recognized or the case proved benign by histologic examination. The term precancerous opens an avenue for the performance of many unjustifiable operations. There are many hundreds of

thousands of badly lacerated cervixes in which cancer does not develop. With our present knowledge of cancer no one can determine which will and which will not develop cancer, but we can definitely state which are cancer and which are not.

There is no proof that any definite precancerous stage exists. There are conditions which are known to predispose to the development of cancer, but to call these precancerous is no more logical than to term the flat-chested, anemic individual pretuberculous, or the sterile negress premyomatous.

For many reasons it may be impossible for a pathologist to make a positive diagnosis from a given slide, and the best that he can do is to state that the histologic picture is suspicious of carcinoma. This is a very different thing than to state that a preparation is precancerous. The latter means that cancer will subsequently develop on tissue now free from the disease and this is an impossible statement to honestly make.

With the advent of radiotherapy in the treatment of different forms of cancer, has come an effort to more closely define the various stages of the disease. This is particularly the case with cervical carcinoma. One of the most satisfactory classifications that has been submitted is that suggested by Schmitz.¹¹ This grouping is based upon clinical findings and is as follows: Stage (i) comprises cases in which the cancer is clearly localized in the cervix; stage (ii) in which doubt exists as to localization. These might be termed the border-line cases. Stage (iii) comprises cases in which there is induration of the contiguous tissue and organ, the so-called inoperable group. Stage (iv) advanced cases, large necrotic craters, cachexia and the "frozen pelvis" and stage (v), recurrence.

This is the grouping that has been adopted in the University Hospital and in the Radiologic Department of the Philadelphia General Hospital, by Ward in The Woman's

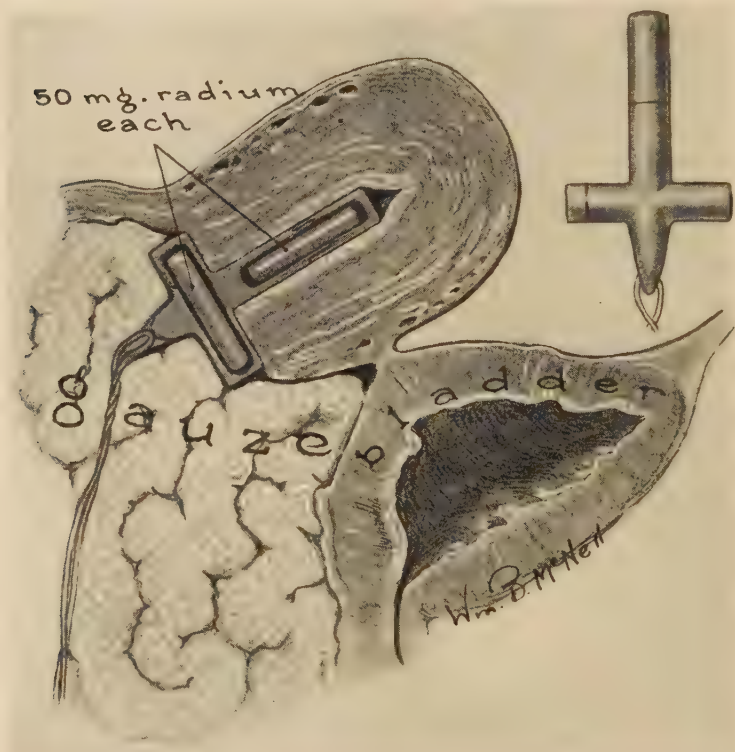


FIG. 29.—Irradiation for an early cervical carcinoma. The bladder has been separated from its cervical attachment almost to the peritoneum. This facilitates the operation and permits wide packing back. A high trachelectomy has been performed with the cautery. The Clark applicator carrying 100 mg. of radium has been applied and stitched in place. The bladder and rectum have been packed out of the field of irradiation by the gauze pack. No effort is made to close the trachelectomy wound. The radium remains in place for 24 hours. In some cases the irradiation is repeated three or eight weeks later. This application is made with brass 1 millimetre thick, with a sheathing of aluminum 0.5 millimetres thick in both tubes. The large end measures 30 mm. and the cross piece 28 mm. In addition to the screening secured by the metal of this applicator, there is also the screening effect of the silver tube, 0.5 millimetres thick in which the radium is contained.

Hospital in New York and is practically that employed by Greenough¹² in his report to the American College of Surgeons.

TREATMENT.—Much difference of opinion exists as to the best treatment for carcinoma of the cervix. Treatment should be based upon an unbiased study of carefully com-

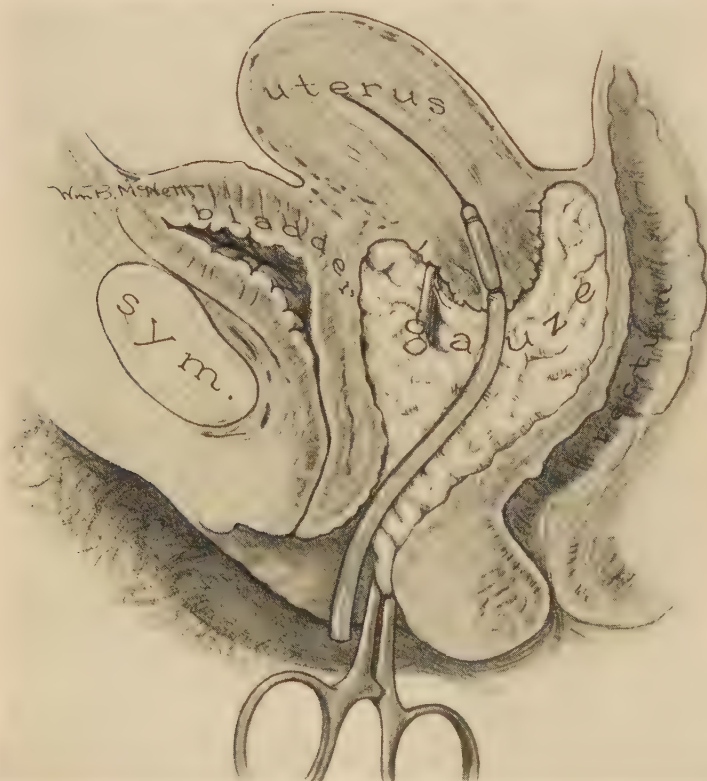


FIG. 30.—IRRADIATION OF A CERVICAL CARCINOMA.—This was an advanced carcinoma (type iii) with involvement of the parametrium and metastases to the pelvic glands. One capsule containing 100 mg. of radium was maintained in position for 24 hours. Complete local healing resulted. Deep X-ray therapy was employed. This patient is free of all symptoms to the present date two years after the initial treatment.

puted end-result statistics formulated from large groups. Whereas the great mass of statistics is honest, many are analyzed from such different points of view that comparison is extremely difficult. It is regrettable that some uniform

system has not been adopted, and the efforts of the American College of Surgeons in this direction is most praiseworthy. The percentage of five-year cures based upon the entire number of cases seen during the same period and the method of treatment are the most important points. Were these two points emphasized as an essential feature in every report it would do much to elucidate the now difficult problem which confronts every surgeon. It is claimed that there is a greater proportion of late recurrences after irradiation than following operation.

A close study of this subject has failed to show any foundation for such a statement. Any period of observation is arbitrary but for many reasons five-year results are preferable to those of three years.

Owing to the more rigid registration systems in force in Europe, five-year results are more easy to secure abroad than with our floating population and for this reason if all lost cases are classed as dead as suggested by some of the German authorities this places the American surgeon at a great disadvantage as far as a comparison of statistics is concerned. In computing statistics, we have more than once placed a lost case in the dead column only to later have the patient turn up alive and well. The same thing has doubtless occurred to many American surgeons when compiling statistics. For this reason, Ward has suggested eliminating lost cases rather than "killing" them and this would appear a more accurate method. The only advantage of counting lost cases as dead would seem to be for the purpose of stimulating a thorough follow-up.

Every student of the cancer problem realizes the vital importance of a thorough follow-up and this argument, therefore, becomes of less importance. However, whatever

method is adopted in regard to lost cases and whatever period is determined upon as a criterion of cure the important part is that they should be uniform in order that an accurate



FIG. 31.—IRRADIATION OF A MODERATELY ADVANCED CERVICAL CARCINOMA.—Trachelectomy has not been performed because of the extent of the disease, size of uterus and fixation of the cervix. The bladder has been separated for some distance from its cervical attachment in order to permit wide packing back. Two capsules containing 50 mg. each of radium have been inserted into the cervical canal and held in place by a stitch. The illustration shows the wide packing back of both bladder and rectum. If a favorable reaction is secured a second application will be made three weeks later.

comparison can be made. The diagnosis of all cases included in statistics should have been verified by histologic examination. The standardization of methods of formulating cancer statistics is an urgent need and offers an opportunity

for some authoritative body such as the American Gynecologic Society or the American College of Surgeons to perform a valuable aid in the advancement of the cancer problem.

Division of cases into groups based upon their advancement is also of importance. This point is, however, somewhat arbitrary and the personal factor cannot be entirely eliminated no matter how specifically the definition of the various stages are defined. Each stage melts into the next and personal opinion is certain to enter into the division of cases to some extent.

At present there are three chief methods generally considered for the treatment of cervical cancer, namely, operation, operation and radium and radium alone or in combination with the X-ray. With the present voluminous and often loosely arranged methods of statistical formulization, apparently convincing proof of the advantages of any one of these methods can be easily secured. It will require at least five years' further study before this question can be satisfactorily answered. If radiotherapy is found to be the most efficient method of treatment, it is possible that the treatment will be largely confined to special hospitals which possess large quantities of the element and the most modern X-ray plants safeguarded by expert physicists and experienced radiotherapists and surgeons familiar with these methods of treatment. The plan is logical and, from a purely scientific and unselfish standpoint, has many advantages.

Much difference of opinion still exists as to the best methods of utilizing radiotherapy. The treatment is, however, gradually becoming standardized, at least on certain points. No method now known for the treatment of cervical cancer is satisfactory. The important point is to select that

which offers the best hope of cure or palliative, according to the conditions of the individual case.

Our opinion, based upon our own results and a careful study of the statistics of reliable authorities, is as follows:

Stage (i). PRELIMINARY TREATMENT.—This comprises the usual physical examination that every preoperative patient should receive, including an examination of the heart,

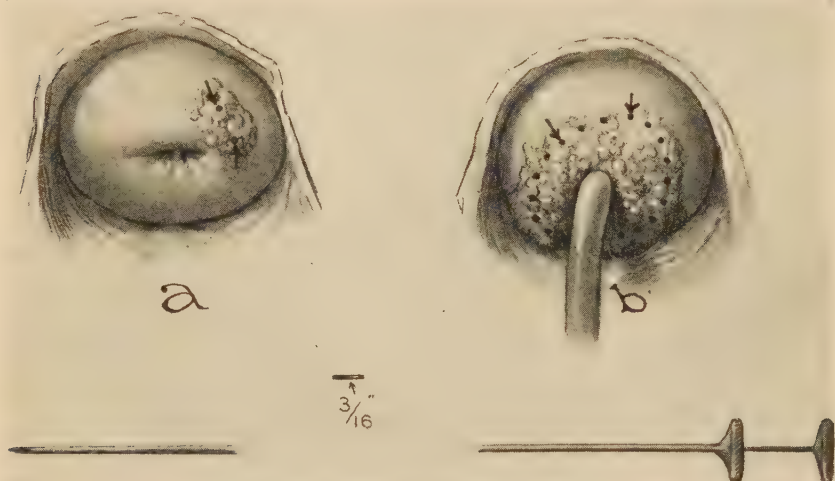


FIG. 32.—SHOWING METHOD OF APPLYING RADIUM EMANATION TO A RECURRENT CERVICAL CARCINOMA.—Each seed represents 0.5–0.5 mg. of radium. Fifty mg. or its equivalent in emanation is introduced into the canal. By means of the trocar, emanation is then introduced as shown.

lungs, urine and blood. If the hemoglobin is low, certainly if below 40 per cent., a transfusion is indicated. The preliminary examinations and treatments should be performed without delay in order that the treatment of the carcinoma may be instituted as soon as possible.

ANESTHESIA.—Although irradiation may be performed without anesthesia, a general anesthesia is decidedly preferable and should be employed as a routine. By its use a more thorough examination is securable and a more satis-

factory application of the radium is possible as well as better safeguarding of the bladder and rectum. Nitrous oxide anesthesia is usually employed, the preliminary administration of $\frac{1}{6}$ – $\frac{1}{4}$ of morphine sulphate by hypodermic one hour



FIG. 33. —PAPILLARY CARCINOMA OF THE CERVIX (STAGE III). —This patient was treated with 2400 mc.h. of radium and later with deep X-ray therapy and is now symptom-free $1\frac{1}{4}$ years after the initial treatment.

before the operation is advisable. For cases in which the examination is difficult on account of rigidity of the muscles, a whiff of ether may be added for this reason. It is important to make certain of the extent of the lesion as far as possible. A short ether anesthesia is well worth while in certain cases.

SELECTION OF THE TYPE OF OPERATION.—In those cases in which the cervix is small, situated high in the vagina, in which the upper vagina is contracted, in which the cervix cannot be pulled down, and in which the lesion is of the ulcerative type irradiation without trachelectomy is employed. If it is possible, by the employment of gauze packing,

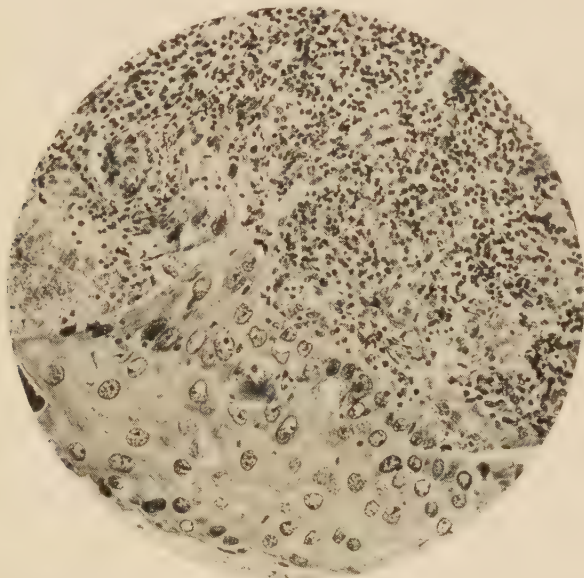


FIG. 34.—Histologic picture from biopsy of case shown in Figure 33 four days after irradiation. Carcinoma cells slightly swollen and marked inflammatory reaction.

to push the bladder wall forward out of the field of irradiation nothing further is done. If, however, it is impossible to pack the bladder back out of harm's way, it may be separated upwards from the cervix for a few centimetres as a preliminary to the irradiation. After the removal of the packing and the radium, the bladder drops back and no stitches are necessary. If conditions are such as to indicate a trachelectomy, the bladder should be separated nearly to the peri-

toneal attachment, care being taken, however, not to enter the peritoneal cavity.

This procedure facilitates the trachelectomy and permits a higher amputation and safeguards the bladder and terminal ends of the ureters. Trachelectomy is now performed as a

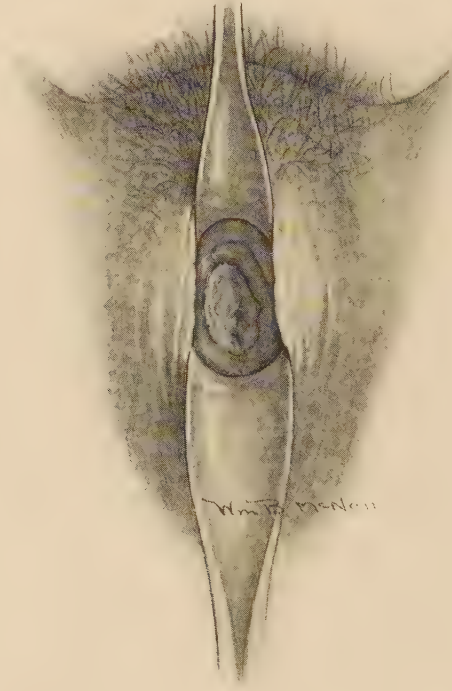


FIG. 35.—Same case as Figure 33, three weeks after irradiation.

preliminary step to irradiation in nearly all early cases. Our most recent analysis shows that radium alone cured 28.5 per cent. of early cases for five years or more, whereas, radium combined with a trachelectomy performed with the cauterity cured for a like period 83 per cent. of early cases (Clark and Ferguson¹³).

Trachelectomy is performed in all cases in which the cervix is easily accessible and there seems to be a possibility of performing an amputation above the level of the carcinoma. When a papillary carcinoma is present, this is removed with the cautery even though a trachelectomy is not indicated, as by its removal a more accurate knowledge of the extent of

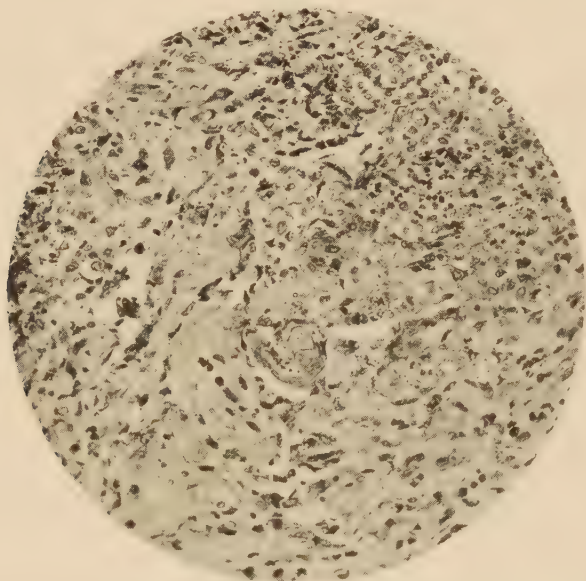


FIG. 36.—Biopsy from case shown in Figure 33, 16 days after treatment. Inflammatory reaction subsiding. Carcinoma cells dropsical, some vacuolated, others show destructions of their nuclei, no mitosis, and an invasion of young connective tissue cells.

the carcinoma is possible, better orientation and more satisfactory placing of the radium is securable. At no stage of the operation is the knife employed except for the primary incision when the bladder is separated from the cervix. At all other times the cautery is substituted. The cautery should be employed at a dull red. This has a tendency to seal off avenues of metastasis and checks hemorrhage. Special effort is made to avoid trauma to the carcinoma and this

applies to the preliminary examinations as well as at the time of operation. For the same reason few sutures are used. The passage of a suture even through macroscopically normal tissues may occasionally be the means of opening lymphatics or blood-vessels and thereby promoting metastases.



FIG. 37.—Same case as Figure 33, showing radium slough five weeks after treatment.

OPERATION.—If a trachelectomy is to be performed, a stitch of No. 2 chromic catgut is passed with a round pointed needle high up on each side of the cervix. These control bleeding and can be used for tractors during the subsequent operation. The bladder is separated from the cervix for a distance of, at least, 2 cm. above the level at which the

amputation is to be performed. The cervix is amputated slowly with the cautery at a dull cherry red. If this is done slowly and the cautery not too hot there should be little bleeding and no vessels requiring ligation. In many cases, carcinoma exhibits a tendency to extend upwards towards the internal os along the mucosa. For this reason the ampu-

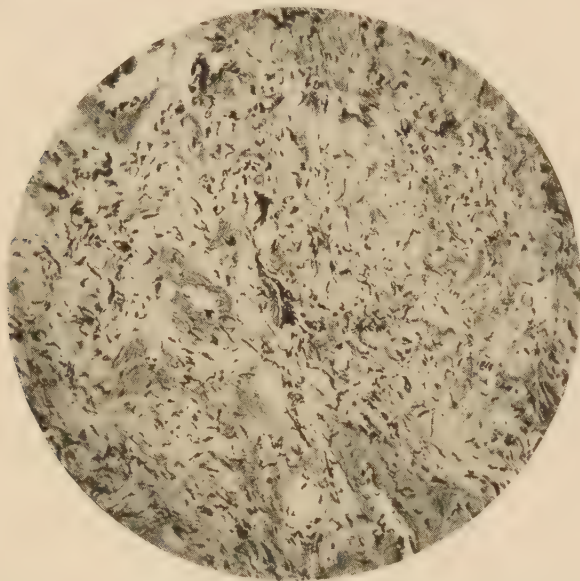


FIG. 38.—Biopsy five weeks after treatment. Case shown in Figure 33. Carcinoma cells have been destroyed. There is a marked new growth of fibrous connective tissue, enmeshed between the fibres of which is the detritus of the nuclei of carcinoma cells as indicated by irregular hyperchromatic material.

tation should be conical. Fifty milligrams of radium is applied in the canal and a like dosage applied to the cervical stump either by means of needles to the musculature or on the face of the amputated cervix. If the later method is selected, the applicator devised by the senior author and shown in the accompanying illustration is a convenient and satisfactory method of making the application.

No effort is made to close the wound in the cervix. After

a cautery amputation of the cervix, the wounds heal by granulation regardless of any effort to close by sutures and the latter are, therefore, useless and may, perhaps, even be detrimental. Occasionally a stitch or two may be used in

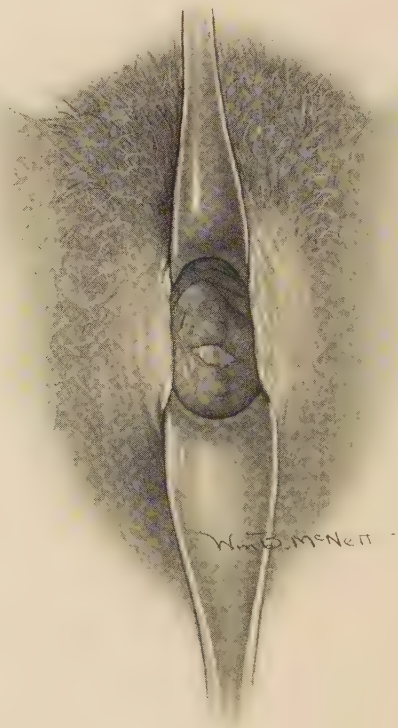


FIG. 39.—Same case as Figure 33, two months after treatment.

order to bring all parts of the cervical stump in close apposition with the radium. This depends upon the exigencies of the individual case but is rarely required. The radium is held in place as shown in the illustration. Two Sims specula are introduced, one along the anterior and the other along

the posterior vaginal wall and by firm retractions and proper tilting of the instruments space is made for wide packing back of the bladder and rectum. The gauze packing remains in place until time for the removal of the radium.

It is sometimes difficult to determine how far upward the carcinoma has extended. In cases of unavoidable amputa-

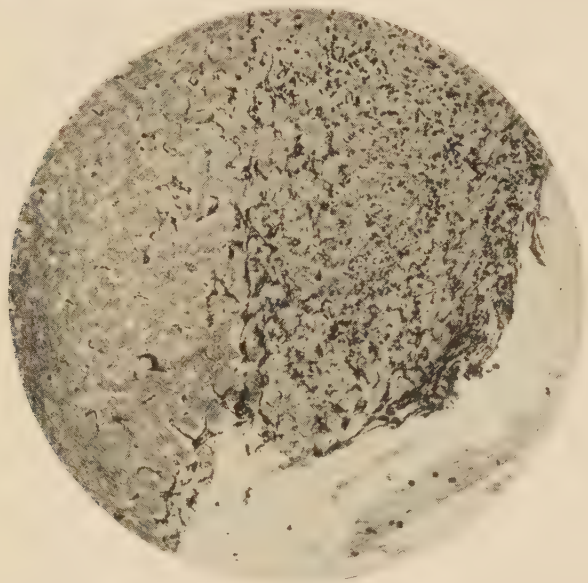


FIG. 40.—Biopsy from case shown in Figure 33, two months after treatment. This carcinoma has been largely replaced by connective tissue. A few irregularly staining carcinoma cells are present in the periphery of the field.

tion through an invaded area special efforts to thoroughly cauterize and irradiate the area are exhibited, generally such an area is near the canal but may be at the periphery of the cervix. In this latter event, radium bearing needles or emanation offer the most satisfactory method of treatment.

When trachelectomy has not been performed a second treatment is generally administered three weeks later either by placing the radium in the cervical canal or by means of

needles or emanation towards the cervical margin or both. If trachelectomy has been performed, a longer interval is usually advisable. Amputations with the cautery heal slowly and it is not advisable to administer a second irradi-



FIG. 41.—Same case as Figure 33, three months after treatment. Complete healing, no palpable evidences of carcinoma. Considerable contraction of the upper vagina. Cervix is shrunken and fibrous.

ation until the reaction incident to the former treatment has to a considerable extent subsided. It is difficult to formulate any rule as to the most favorable time at which to give the second treatment and much depends upon the reaction in the individual case. If a second treatment is to be applied, it should be given as soon as is compatible with safety. If the

treatment is given during the period in which the reaction from the former treatment is active the hazards are materially increased; if, on the other hand, the second treatment is delayed too long valuable time may be lost in which the disease may extend in the deeper structures. We formerly gave the second treatment after a six weeks' interval; at that time



FIG. 42.—Biopsy from case shown in Figure 33. Complete local healing. No cancer cells present. Three months after treatment.

contraction of the upper vagina incident to the primary treatment enhanced the likelihood of vesical and rectal reactions or even actual burns. With a three weeks' interval, the contraction incident to the primary irradiation is much less marked. At the second treatment, the bladder may again be separated from the cervix if this seems advisable. It is decidedly preferable to incur the minor inconvenience incident to this procedure than to cause a fistula or even a

radium reaction to the bladder. For some time we made only one application of the radium but have recently been employing a second as described. Ward and Farrah¹⁴ utilize the first treatment as a sort of test and decide whether subsequent applications shall be administered largely by the reactions to the initial irradiation. The reaction at the end of three weeks is of distinct prognostic value. The cases are subsequently observed at three-week intervals for the first three months and later at somewhat longer intervals but never longer than ten weeks. If any suspicious area is observed, this is treated by radium-bearing needles or emanation. This follow-up is of extreme importance and the examination should be made by an experienced person, preferably the chief.

The advantages of subsequent cross-firing by deep X-ray is one upon which we are still undetermined. In the Radiologic Department of the Philadelphia General Hospital this procedure has been employed routinely, whereas at the University Hospital it has only occasionally been adopted. We believe that, speaking generally, deep X-ray therapy has not, in this country at least, lived up to its promises. On the other hand, when carefully controlled, its dangers are slight and the discomfort to the patient minimum. There is no one dosage satisfactory for all tumors. Within certain limits dosage can be defined. The amount of irradiation required to successfully destroy an unripe tumor may be considerably below an adequate dose for a neoplasm composed of a more adult type of cells. As Ewing¹⁵ states, the differentiation between embryonal and cellular anaplastic tumors is important and until this is done the radiologist will continue to meet surprises and disappointments. Furthermore, the location and size of the tumor must be taken into consideration.

It is apparent that improvement in end-results will not be along the line of greatly increasing the amount of irradiation now in use.

Much has been written upon the so-called "killing" dose of radium and there are in the literature many references to "cancer dose" and "sarcoma dose." It may here be recorded that radium produces its action in three ways, namely autolytic degeneration, particularly noticed when applied to the unripe type of tumor, a caustic action and finally, growth restraint. Ewing¹⁶ states that he is convinced that the clinical results are not usually due to the direct killing effect of radiation, but are generally brought about indirectly. It seems probable that slow autolysis and growth restraint, aided by the natural defense reaction of the body, combined to bring about gradual regression and eventual disappearance of the tumor. We do not believe that increase of dosage will result in better end-results. There is no appreciably marked difference in the end-results from those clinics employing an extremely large dose than from those using more moderate amounts. Indeed some of the best end-results statistics come from clinics possessed of relatively small amounts (100–200 mg.) of radium.

Each tumor is a study in itself. There will probably never be a "cancer dose" developed, as the correct amount of irradiation is dependent upon so many factors. Lahm¹⁷ states that statistics show the most favorable dose is 6000 mg. Schmitz¹⁸ recommends 110 to 130 per cent. of the E. S. D. Seitz and Wintz give 90 to 110 per cent. of the E. S. D.

It has been suggested that the abdomen be opened in order to more effectually irradiate the tumor and define its extent. This procedure has not appealed to the writers. It is probable that if the disease has spread to such an extent

that it cannot be reached from below, little can be gained by an abdominal section even were we to disregard the added likelihood of an increase in the primary mortality, morbidity, and discomfort to the patient, and longer hospitalization. The results which have been secured by this method are at present certainly no better than those which have been attained by less radical measures.

For the capable surgeon, whose experience with radiotherapy is limited or to whom an adequate supply of radium is not available, hysterectomy is decidedly the treatment of choice. Lynch¹⁹ states that the ordinary panhysterectomy has no place in the treatment of cervical cancers. On the other hand, the radical operation is one of the most difficult in pelvic surgery and should certainly not be attempted except by an experienced pelvic surgeon. We believe that radiotherapy or radiotherapy in combination with X-ray is decidedly the most satisfactory method for all cases. If it is accepted that irradiation alone will cure a greater number of the advanced cases than will operation, it is somewhat illogical to recommend operation for the early cases unless its application in the former group is considered as purely palliative and all such cases doomed. Our belief is that operation in any but stage i cases is, apart from the operative mortality and complications such as injury to the ureter, bladder, etc., almost certainly followed by recurrence, whereas, experience has demonstrated that radium offers better end-results and is associated with far less immediate mortality and morbidity, and, in addition, is the best palliative treatment at our command.

Stage ii or border-line cases are treated in the same manner as stage i cases, except that trachelectomy is not such a routine procedure. In the papillary types where the

presence of the tumor mass interferes with the satisfactory placing of the radium the obstructing neoplastic tissue is removed with the actual cautery at a dull heat. Although it is often employed, we are not routinely administering a second irradiation, but depending largely upon the character

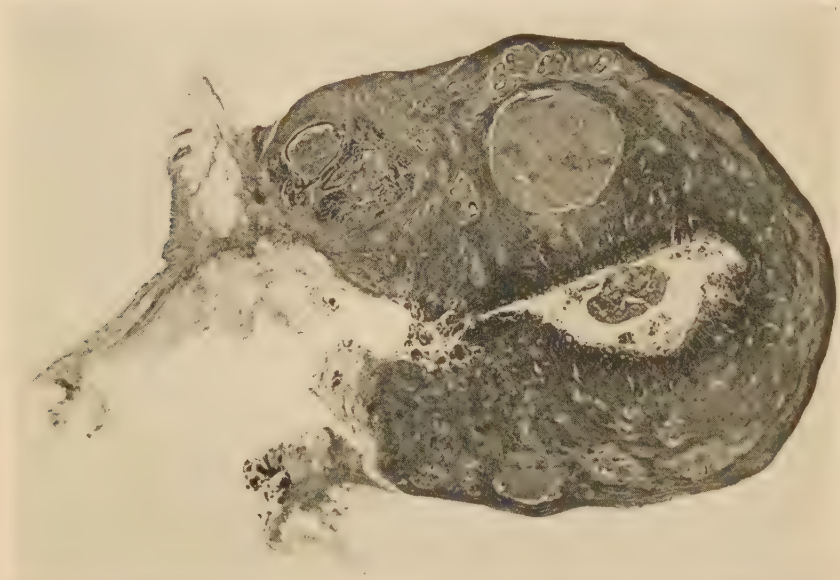


FIG 43.—Epidermoid carcinoma of the cervix. Stage iii showing effects of irradiation. The ulcer involving the upper third of the vagina and cervix show necrosis but no carcinoma. In the posterior lip of the cervix is an area of active carcinoma apparently unaffected by the irradiation. A smaller similar area is present in the anterior lip. A small dosage of radium was given in this case for its palliative effect (1300 mg.h.) two months before death.

of the individual case and the reaction of the neoplasm to the primary treatment.

Stage iii or definitely inoperable cases are treated with a single dosage of 2000 to 2500 mg., provided this can be applied without undue risk of the production of a rectal or vesical fistula. This is nearly always possible. Occasionally, however, cases will be encountered in which the involvement is such that any effort to irradiate is almost certain to pro-

duce one or other of these complications. Under such circumstances irradiation is not advisable. These cases are practically hopeless as far as ultimate cure is concerned, and irradiation is at best only a palliative procedure. The discomfort of a fistula in such a patient far outweighs any palliative results that can be secured. Obstructing papillary growths are removed with the cautery as in stage ii cases.

Stage iv cases are not subjected to irradiation. Irradiation cannot be efficiently employed and attempts to treat by means of either radium or X-ray only subject the patient, who is already doomed, to further discomfort, and may actually shorten life.

Stage v cases or recurrences, either from operation or previous irradiation, usually present an unfavorable prognosis. Much, however, depends upon the individual case. This does not include small, undertreated areas sometimes observed during the regular irradiation cycle. As a rule, patients in the fifth stage are best treated with the emanation or, lacking this, with radium needles, the dosage depending upon the location, size and variety of the lesions and whether previous irradiation has been employed. Dosages of from 1500 to 2000 mc.h., in some instances repeated in four to six weeks, usually effect a local healing.

The possibility of danger resulting from ill-advised or performed irradiation had been stressed. In properly selected cases and careful technique, irradiation actually safeguards the patient against these unfortunate complications. In the Radiologic Department of the Philadelphia General Hospital most advanced cases are seen; 50 per cent. of the cases have been treated in other institutions prior to coming to us. In all we have treated 289 cases, all of whom, with two exceptions, were in stage iii, iv or v. In this series there have

been three fistulae which developed after treatment and that may have resulted from irradiation. Among the last 320 cases treated at the University Hospital, not a single fistula occurred as a result of the treatment. A small percentage of fistula will occur as a result of the disease and not due to irradiation. We therefore repeat our previous statement that, when properly applied, irradiation actually shields the cancer victim against this distressing accident.

For the stage v cases deep X-ray therapy to the parametrium is advisable, unless the case is evidently hopeless. By this treatment Bailey²⁰ has salvaged 19 per cent. of early recurrences for from three to six years.

As previously stated, unless a definite contraindication exists, a general anesthesia is advisable. Markedly anemic patients usually suffer a greater reaction and generally do not do so well following irradiation; for this reason a preliminary blood transfusion is recommended. Farrar²¹ uses a self-retaining catheter in the bladder while the radium is in place. Whereas it is important to avoid distention of the bladder during this period in order to minimize the danger of injury to this organ, we prefer a routine catheterization at six-hour intervals. Many of these patients are able to void at once and the majority do not require the use of the catheter more than once or twice.

At the time of the operation a piece of the neoplasm is removed for microscopic examination as a routine procedure, provided biopsy has not been previously employed. This piece of tissue should not be less than 1 cm. in diameter and should be excised from the edge of the tumor and should include a part of the macroscopically normal cervix or adjacent structure. Beginning a few days after the irradiation, daily vaginal douches are given for cleansing purposes. Weak

potassium permanganate or weak formalin solution is excellent for this purpose and are good deodorants. As the discharge diminishes, the frequency of the douches may be reduced, and where local healing has occurred they may be entirely discontinued.

Regulation of the bowels, an abundance of nourishing

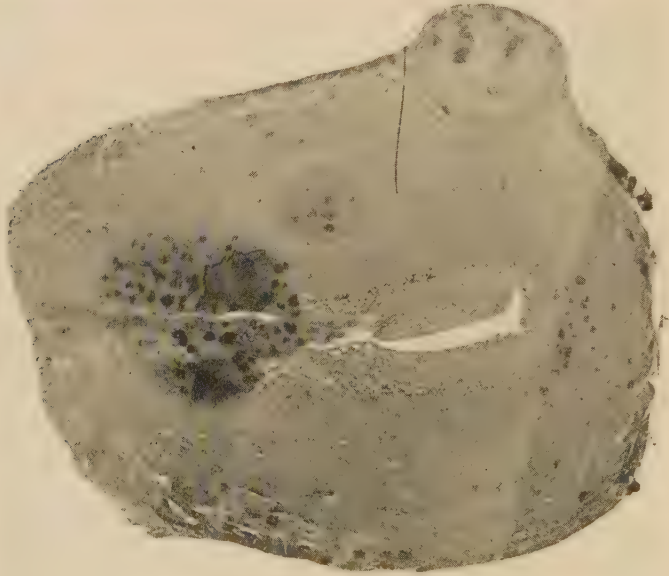


FIG. 44.—Adenocarcinoma of the cervico-uterine junction showing area of irradiation. Diagnostic curettage and irradiation followed by panhysterectomy one month later. Apparently complete destruction of carcinoma by irradiation. No evidence of recurrence $2\frac{1}{2}$ years later.

food, general attention to hygiene and an effort to build up the general health and resistance of the patient are of importance as postoperative measures. As already indicated, the follow-up of these patients is of the utmost importance. This point is explained to the patient and her relatives before she leaves the hospital and on her discharge she is given an appointment indicating the day and hour on which she is to

make her first return visit. Among ward patients the services of a competent social service worker are essential. The majority of these cases feel so much improved or are so entirely symptom-free after a few weeks that unless they are followed very carefully, a proportion at least will drift away and fail to finish their course of treatment and be lost sight of for end-results study. At the University Hospital and in the Department of Radiology of the Philadelphia General Hospital, the follow-up departments are thoroughly organized. In a recent study at the latter institution, of the entire series of 289 cervical carcinomata covering the last three years, not a single case had been lost sight of, and during the last year at the former institution, the general follow-up on cases of malignant neoplasm was 98 per cent.

We have not been impressed with the advantages of preoperative irradiation; apart from the loss of time irradiation tends to devitalize the normal tissue. After the stage of connective tissue formation produced by the action of the radium, operation may liberate encapsulated carcinoma cells and accelerate recurrence. Those cancer cells, which are destroyed by the irradiation, are harmless and their removal unnecessary. In a few cases in which we have employed preoperative irradiation the results have been unsatisfactory and we have discontinued the method.

Those who are known to have access to radium are frequently requested to give postoperative treatment to patients upon whom a hysterectomy has been performed by other surgeons. Many of these cases are referred because the surgeon feels doubt regarding the removal of the entire tumor. One of the reasons that we prefer a high trachelectomy to hysterectomy as a preliminary procedure is that the uterine cavity left by the former type of operation offers

such an excellent site for irradiation and the parametrium may be safely utilized for the treatment by emanation or needles.

If on the other hand a hysterectomy is performed, the postoperative application of an efficient dosage of the element cannot be applied with the same safety. Under such circumstances the danger of injury to the bladder, rectum, adherent loop of intestine or ureter is greatly enhanced. These patients are generally best treated by full doses of deep X-ray as soon as complete resolution has occurred. They should be cross fired, paying especial attention to the parametrium and region of the pelvic glands. Bailey²² has treated 14 such cases, 63 per cent. of whom are alive for three or more years. These postoperative or prophylactic treatments, given soon after operation, are in a quite different category than those cases who suffer a definite recurrence after hysterectomy; the latter offer a much more unfavorable prognosis. In the latter type much depends upon the character of the recurrence; palpable nodules can often be benefited by the use of emanation or needles as already stated, and deep X-ray may occasionally hold the metastasis in check. The outlook is, however, at best unfavorable.

CANCER OF THE CERVIX AND PREGNANCY.—This is an infrequent combination although cases are occasionally observed. Under these circumstances, the diagnosis of carcinoma is often more difficult than when pregnancy is not present. During pregnancy especial care should be exercised not to mistake benign lesions of the cervix for cancer. The increased vascularity of the cervix incident to gestation must be taken into consideration. This congestion often causes benign lesions such as lacerations with eversion to take on many of the clinical characteristics of carcinoma.

Extensive eversion of the cervix of the pregnant uterus often appears to increase in size and frequently bleeds rather readily after trauma. If any doubt exists as to the correctness of the diagnosis biopsy should be performed without delay.

Cervical carcinoma occurring with pregnancy usually exhibits a more rapid growth and earlier metastasis than in the non-pregnant uterus. This increased malignancy can probably be accounted for largely by the greater vascularity of the lesion incident to pregnancy and to the fact that these patients are generally among the younger of the women afflicted with cervical carcinoma. The disease is generally more malignant in young than in old individuals and these patients have this added factor against their ultimate recovery.

TREATMENT.—This varies with the stage of the advancement of the carcinoma and the duration of the pregnancy. During the first three months of pregnancy it is generally advisable to disregard the pregnancy and treat the carcinoma as if pregnancy were not present. If the carcinoma is an early one the treatment previously indicated for tumors in this stage is appropriate. At the time of the treatment the evacuation of the uterus should be performed either by curettage or an anterior vaginal hysterotomy according to the conditions present in the individual case. Very early pregnancies are generally satisfactorily evacuated by means of the curette. Pregnancy advanced to three or four months especially if the cervix is to be amputated and the uterus can be pulled well down is usually most satisfactorily treated by an anterior hysterotomy performed in combination with the irradiation.

If the uterus is not emptied, the chances of securing a living child are, in any event, reduced. The likelihood of abortion as a result of the treatment of the carcinoma is

considerable incident to the vigorous treatment and, perhaps, repeated irradiation, and if abortion does not follow, the chances of premature labor, dystocia, severe lacerations of the cervix and hemorrhage are too great to warrant a continuance of the pregnancy.

The combination of an early pregnancy and an advanced cervical carcinoma is an even more unfortunate one. Such cases must be individualized, the pregnancy can generally be disregarded as the death of the mother is likely to occur before the child is sufficiently matured to be saved. On the other hand, evacuation of the uterus is often hazardous, due to the likelihood of infection, severe lacerations of the cervix and hemorrhage. When it is possible the evacuation of the uterus is advisable. Irradiation, as previously described, is indicated.

From the fourth to the sixth month of pregnancy, there is a naturally somewhat better chance to saving the infant by a Cæsarian section either at or sometime before term. At this time, therapeutic abortion is of itself a more hazardous operation, a greater dilation of the cervix is necessary to empty the uterus with its accompanying likelihood of laceration, hemorrhage and infection. If the carcinoma is an early one and the cervix and tumor such as to make an amputation with the cautery easy, this procedure, combined with an anterior hysterotomy and evacuation of the uterus and adequate irradiation give the patient the best chance of a permanent cure. As a result of the hysterotomy, the bladder has been freed from the anterior uterine wall and safe packing back of the former can be easily accomplished. In some cases, irradiation alone followed by Cæsarian section if the pregnancy goes to, or nearly to, term is the treatment of choice.

In the cases in which the carcinoma is more advanced, irradiation with 1500–2000 mg.h. of radium, and, if a favorable reaction of the tumor occurs, a repetition of the treatment a month or two later followed by Cæsarian section performed as early as is compatible with the welfare of the infant is the most satisfactory method.

During the later months of pregnancy the life of the infant should be definitely taken into consideration. If the carcinoma is in an early stage irradiation with a full carcinoma dose is called for, as of the two the mother's life is always the most important. If the carcinoma is advanced it may in some instances be preferable to avoid all treatment to the cancer until such time as a Cæsarian section and a living child can be secured, the Cæsarian section naturally being performed as early as is compatible with the welfare of the infant. As an accompaniment of the Cæsarian section appropriate irradiation treatment should be applied.

In the early months of pregnancy irradiation under a full cancer dose may produce abortion even provided no wide dilatation of the cervical canal is necessary. Generally, this is not the case. There is, however, no uniformity of opinion upon this point. Deep X-ray therapy to the pelvis during the early months of pregnancy generally produces abortion in from 5 to 40 days. Irradiation of the cervix by means of radium is less likely to result in an interruption of pregnancy. M. Schockaert²³ believes irradiation to a pregnant woman is almost certain to cause abortion. On the other hand, Hen-votay²⁴ of Antwerp and others of wide experience believe this rarely to be the case. In any event, if the patient can be carried to, or nearly to, term abdominal Cæsarian section should be performed. Attempts to deliver through a carcinomatous cervix are unsatisfactory and generally result in

deep tears, hemorrhage and are often followed by sepsis, and if irradiation has produced a local healing the contraction of the upper vagina and cicatricial condition of the cervix are almost certain to result in dystocia if vaginal delivery is attempted. For these reasons, Cæsarian section should be performed before the onset of labor and generally speaking, as early as is compatible with the welfare of the infant.

TREATMENT OF CARCINOMA OF THE CERVICAL STUMP.—Carcinoma may develop in the cervical stump left behind after a supravaginal hysterectomy. This fact has been advanced as an argument for panhysterectomy as a routine procedure when it is advisable to remove the fundus of the uterus. Prophylaxis against cancer is of the utmost importance and were the development of cancer frequent in such cervical stumps total removal would undoubtedly be the operation of choice in all cases. Our experience has been that cancer develops in the cervical stump in about the same frequency as it does in the cervix upon which supravaginal hysterectomy has not been performed. Even in the most skilled hands panhysterectomy carries with it a somewhat higher mortality than does the less radical operation.

Furthermore, the supravaginal hysterectomy has no tendency to shorten the vagina and diminishes the likelihood of prolapse of the upper vagina. In the Gynecologic clinic of the University of Pennsylvania our practice has been to perform panhysterectomy upon those cases in which marked pathologic lesions of the cervix have been present or in which leukorrhea has been a prominent symptom but to conserve the cervix when the latter was normal. This policy is based upon the belief that the added mortality and morbidity incident to a panhysterectomy more than counter-balanced the incident of the occurrence of carcinoma in cervical

stumps which were comparatively normal at the time of the hysterectomy.

The treatment of carcinoma in the cervical stump is governed by the same general principles as when the disease originates in a cervix upon which the fundus is present. One of the dangers in the treatment of cancer of the cervical stump which is not present in the ordinary case is that a loop of intestine may be adherent to the top or posterior aspect of the stump and may be injured by the irradiation. On one occasion in which doubt existed upon this point a small incision was made in the culdesac to ascertain the conditions present as a preliminary step to the irradiation. The shortness of the cervical canal may also be a handicap to the proper placing of the radium in those cases upon which an unusually low amputation has been performed. Separation of the bladder in order to safeguard this organ and the lower ends of the ureters, as previously described, is often advisable. If doubt exists as to the ability to safeguard surrounding structures a slightly smaller dosage of radium may be employed and a second or even third application of radium may be given if the neoplasm responds well to the primary irradiation. Emanation rather than the actual radium is often preferable and applications to the vaginal surface of the tumor are safer than those applied deep in the canal.

RESULTS.—Glowing reports regarding treatment of cervical carcinoma by means of radium or deep X-ray therapy, or combination of these methods, have been received from some of the European clinics. Thus Von Seuffert²⁵ claims 80 per cent. of five-year cures in his early cases which took the entire course of treatments. This consisted of both radium and X-ray. Von Seuffert states that the hysterectomy for cervical cancer has been abandoned in

the Doederlein Clinic since 1913. More recent statistics from the Doederlein Clinic are given by Voltz²⁶ as follows: 755 five-year patients were treated, 110 were operable with 43.6 per cent. of cures, 130 were border-line cases with 22 per cent. of cures, 340 were inoperable cases with 6.7 per cent. of cures, 169 were hopeless cases with one cure, 6 cases are not accounted for.

Lynch and Maxwell²⁷ have made a comprehensive review of the literature pertaining to this subject and it is from this work that many of the following figures have been secured: Von Seuffert's statistics come from the Doederlein Clinic in Munich. He compared the five-year results in a series of 500 five-year cases treated by irradiation to a series of 265 five-year cases treated by hysterectomy, the irradiation results being about twice as good in the entire series. So far as we are aware such results have never been secured or even approached elsewhere in any large series of cases. Of far greater value is the carefully controlled results tabulated by Heymann²⁸ from the Radiumhemmet in Stockholm. This author records the results secured by irradiation in 505 cases. Each case counted as a cure was examined by Heymann five years or more after treatment, the cases being brought back to Stockholm for examination by a government grant. All cases not examined were counted as cancer deaths. Two hundred and seventeen cases were available for five-year study. Five-year cures were secured in 40.5 per cent. of the 19 operable cases, 16.6 per cent. of cures (symptom free) occurred in 181 inoperable or border-line cases. Treatment was refused to 7.5 per cent. of cases. The immediate mortality was 1.2 per cent. of the entire series. The same amount of radium salt was used for the same length of time at each treatment. In all, three treatments were given, the second

one week after the first and the third three weeks after the second. The three treatments amount to 2400 milligram hours in the uterus and 4500 milligram hours in the vagina. A screen of 2 mm. of lead was used in the uterus and a screen of 3-4 mm. of lead or its equivalent in the vagina. Heymann does not state the number of fistulæ which occurred.

Seitz²⁹ reports the results secured in 58 cervical carcinomata; of this series 20.9 per cent. were alive at the end of five years. In the group were eight early cases, of which four were symptom-free five years later. Seitz employed small doses of radium and X-ray. He quotes from the literature the results secured by others: Baisch, 42 cases, 16 per cent. of five-year survivals; Klein, 73 cases, 12 per cent.; Beuttner³⁰ from Geneva, 63 cases, 17 per cent.; of these nine were early cases with four- to five-year survivals, eight were border-line cases, four survivals, 25 were advanced with three survivals. Philipp and Gornick³¹ report that of 206 cases submitted to the radical operation six of whom were previously irradiated, 40.79 per cent. were free from recurrence five years later. A proportion of these patients were given postoperative X-ray treatment. The primary mortality from the radical operation was 14.92 per cent. The favorable results of the series is attributed by the authors to the fact that, as a rule, only the favorable cases were operated upon, whereas the advanced cases were treated by radium. Of 805 cases of the cervix treated by irradiation 180 were operable, 379 inoperable and 226 border-line. 15.27 per cent. were cured, 28.33 per cent. of the cured cases were in stage i and 5.76 per cent. were inoperable. The incident of cure in the operable cases treated by irradiation was 38 per cent.

Of more interest to American readers are the results

secured at home. Perhaps the most important report from this country is that presented by Greenough³² in 1924. This consists of a preliminary report of a committee appointed by the American College of Surgeons. The material embraces 826 cases of cervical cancer from the leading clinics of the country. The end-results must be discounted to an extent in that they are based upon three-year and not five-year statistics. These studies showed slightly better results in early cases for hysterectomy than for irradiation. In all except the early cases, treatment by radium was superior.

Clark and Ferguson³³ in the study of 214 cases found the following results: All cases were treated by irradiation and some of the more favorable by radium and cautery amputation—13.8 of the traced cases survived five years or more, of 161 three-year cases 16 per cent. survived. Of those who were treated within six months from the time appearance of the first symptom 60 per cent. were in stage iii or iv. A case treated after the first six months has one chance in 26 of a five-year cure. Irradiation alone cured 28.5 per cent. of stage i cases. Irradiation combined with a cautery trachelectomy cured 83 per cent. of similar cases for a like period. There were no five-year survivals among the stage ii cases treated by radium or radium and cautery. Among the stage iii irradiation alone cured 5.1 per cent. for a five-year period, irradiation and cautery amputation cured 20 per cent. In all cases, irradiation alone cured 5.9 per cent. for five years with an operative mortality of 1.4 per cent., irradiation and cautery amputation 42.9 per cent. with an operative mortality of 10.6 per cent. Irradiation or irradiation and cautery amputation relieved hemorrhage and discharge either temporarily in 75 per cent. of cases. As a rule, pain was relieved by the treatment, in a proportion of the cases

pain was increased after irradiation. The average duration of relief of symptoms was one year.

Schmitz³⁴ states that, of 103 primary carcinomata treated by him, 14.5 per cent. were symptom-free five or more years later; of 48 cases with recurrence, stage v, cases treated during the same period, but 4.5 per cent. were salvaged.

Ward and Farrar³⁵ report 72 five-year cases of which 14.6 per cent. were cures by the use of radium alone. They also record 43.6 per cent. of relative (three-year) cures. Farrar³⁶ states that they were unable to trace eight cases and that these have been deducted instead of "killed." Doubtless some of these were three-year cases and did not belong to the group from which the above statistics were formulated.

Muhlmann,³⁷ after reviewing the literature, states that there are 10-20 per cent. of permanent cures following irradiation for inoperable cancer. Lahm,³⁸ after a similar review a year later, concludes that 34 per cent. are permanently cured.

Much divergence of opinion exists regarding the merits of combining deep X-ray therapy with irradiation by radium. Zweifel,³⁹ at the meeting of the German Gynecologic Congress in 1922, stated that the results of Doederlein, during the years 1917 and 1919, were improved 6 per cent. for operable cases and slightly more for inoperable cases by the addition of X-ray therapy. Bumm⁴⁰ reported in 1922 13 per cent. of cures of 22 operable cases by X-ray alone. Amann⁴¹ reported from Munich an improvement of from 39 per cent. to 61 per cent. in a series observed for less than five years. Many of the statistics previously quoted have been secured by a combination of these methods, although as previously stated, deep X-ray therapy has not, in this country at least, lived up to its heralded reputation.

The majority of large European clinics treating cervical cancer by radium are also employing deep X-ray therapy. Heymann⁴² formerly employed X-ray but has now abandoned its use as he believes as good results are obtained by radium alone. Deep X-ray therapy does not greatly add to the immediate mortality and the worst that can be said of it is that the reaction may be unpleasant. Carefully administered the proportion of severe reactions should be small. It would appear that at least a slightly greater percentage of five-year cures can be obtained by its use. It is needless to state that deep X-ray therapy is quite as dangerous in inexperienced hands as would be attempts to perform the Wertheim operation by the novice.

Schmitz⁴³ states if we use radium without X-ray in cervical cancer we are at a disadvantage due to the rapid decrease of the intensity and therefore inhomogeneous distribution of the rays. The regional lymphatics cannot be effectually destroyed. If we employ X-ray without radium then we are limited by the tolerance of the skin to a low dose though a homogeneous distribution of the rays throughout the pelvis is attained. However, if we use a combination of radium and X-ray we can obtain a homogeneous distribution of a radiation intensity throughout the pelvis.

It has been claimed, with some reason, that the amount of reaction may be taken as a guide to the susceptibility of the tumor to the action of the rays. Intoxication is apparently due to the absorption of broken down cells. For literature see Schmitz.⁴⁴ The former statement is, however, only partially true for Ewing⁴⁵ has stated the ideal dosage is capable of restraining the growth of the neoplastic cell without causing either autolysis or necrosis; however, tissue breakdown often does occur.

Reactions are best treated symptomatically, rest in bed, the administration of copious quantities of fluid and stimulation of the action of the kidneys and bowels. Acidosis requires alkalinization and alkalosis the exhibition of mild acids such as lemon or orange juice. Nausea and vomiting may be relieved by morphine and atropin or in severe cases by lavage. Hyperdermoclisis or even transfusions may be employed in severe cases.

In the foregoing pages some of the results secured in the treatment of cervical carcinoma by means of irradiation have been quoted. At best these are far from satisfactory. The important point is, however, how they compare with reliable statistics formulated from the other recognized method of treatment—radical hysterectomy. Faure⁴⁶ reports 50 per cent. cures by the radical operation; Wertheim,⁴⁷ 43 per cent.; Bumm, 49 per cent. The two latter are based upon the number of operable cases and not the total number applying for treatment. Johns Hopkins Hospital,⁴⁸ 26.6 per cent.; Stoeckel,⁴⁹ 26.6 per cent.; Graves,⁵⁰ 18.5 per cent. As will be observed, surgical statistics vary as widely as do those relating to irradiation. In comparing the two Polak⁵¹ states that in this country the primary operative mortality for the radical operation ranges from 8 per cent. to 20 per cent. A 10–20 per cent. mortality may be expected in the hands of the average surgeon. Thirty per cent. of five-year cures is about all that can be claimed for the radical operation even by the best American operators.

We believe that many of the operations called radical fall short of the best teaching regarding this operation and that relatively few surgeons are capable of performing a satisfactory Wertheim operation. Even in really capable hands, the Wertheim operation, utilizing only selected cases, is a

formidable operation and associated with a high operative mortality and a high proportion of morbidity as instanced by injury to the ureter, bladder and other vital structures. The radical operation requires extensive dissection, produces much trauma, results in a wide exposure of cellular tissues and opens avenues for infection and peritonitis. It is well known that virulent streptococci are frequently present in these cases. The possibilities of trauma, metastasis or implantation growths must also be borne in mind, as well as the effects of prolonged anesthesia, loss of blood, hemorrhage and shock, and other factors contributing to a high operative mortality. Hospitalization is often prolonged and in the most favorable cases is two or three times that required for irradiation.

The general trend of the American surgeons is away from the Wertheim type of operation. This is based not so much on its high mortality and morbidity as upon the study of the end-results, which show that when the disease has extended beyond the cervix and when metastasis has developed, the five-year salvage is extremely small and does not overbalance the disadvantages of the radical procedure. On the other hand, if the cancer is confined to the cervix the same proportion of cure can be secured by less hazardous procedure.

The radical abdominal hysterectomy for cancer of the cervix was suggested by Reis and Clark, and was later popularized by Wertheim through his extensive application of the principle and the perfection of its surgical details. Clark's personal interest in this operation was engendered through the decided improvement in results following the application of the radical removal of the breast and its attending axillary dissection as suggested by Halsted. Clark championed the radical operation and as time ulti-

mately proved, the final statistics from the clinics of this country and Europe, following its adoption, were the best hitherto published, but the primary mortality was high in all hands and shocking in many. Furthermore, the relatively low percentage of operability cut deeply into the actual proportion ultimately saved.

It is recognized that no further progress is possible from still more radical surgical procedures, for the utmost anatomic results have been reached. The radical abdominal operation has been thoroughly tried and at best the end-results are far from satisfactory. From the anatomic standpoint radical operation is hedged about with difficulties. The cervix is closely surrounded by vital structures, ureter, bladder and rectum, none of which can be sacrificed, and injury to any of which is disastrous. The longer hospitalization and prolonged convalescence are also factors to be considered. Were it possible to show, however, that the radical operation actually produced better end-results these naturally should outweigh all other considerations. On the following page may be found a table compiled by Clark and Block,⁵² showing the results of operation from ten surgical clinics.

It would seem generally accepted that irradiation is the preferable form of treatment for all but the very early cases and by it a greater percentage can be carried to the five-year period, and in the remainder life is usually prolonged and made more bearable.

It is among the stage i cases that advocates of surgery still advise operation. The radical operation gives about the same end-results in the small group of early cases. Von Franke,⁵³ 80 per cent. surgery; Von Seuffert,⁵⁴ 80 per cent. irradiation, to quote the most favorable. The average operator, however, cannot hope to secure these results, and

his results, even in the earliest cases, are probably no better, if as good, as those secured by irradiation. Polak⁵⁵ states that in New York 20 per cent. of cases are seen in the operable stage: in Philadelphia we see less than 10 per cent. However this is an arbitrary question, for what one surgeon considers operable may be viewed differently by another. All authori-

RADICAL OPERATION FOR CARCINOMA OF CERVIX

Name of Operator	Journal	Total Applying	Operability Per Cent.	Number Operations	Primary Mortality Per Cent.	Five-year Cures Per Cent.
Martzloff . . .	Bull. Johns Hopkins Hosp., 1923, xxiv, 141.	387	46	178	14.2	26.6
Mayer	Zentralbl. f. Gynäk., 1920, xlv, 617.	725	65.3	457	20.3	39.3
Cobb	Jour. Am. Med. Assn., 1920, lxxiv, 14.			35	14.3	57.1
Graves	Surg. Gynec. and Obst., 1921, xxxii, 504.	189	64	119	5.0	34.2
Bonney	Brit. Med. Jour., 1921, ii, 1103.			100	20.0	42.3
Peterson	N. Y. State Jour. Med., 1920, xx, 313.	380	15.7	60	26.6	40.9
Schweitzer . . .	Zentralbl. f. Gynäk., 1921, xlv, 289.	443	40.0	177	6.78	51.4
Davis	Ann. Surg., 1922, lxxvi, 395.	85	37.6	32	9.3	40.0
Giesecke	Arch. f. Gynäk., 1922, cxv, 435.	371	70.6	224	19.6	33.5
Bumm	Zentralbl. f. Gynäk., 1919, xlv, pt. 1, 1.			157		49.0

ties, however, agree that the proportion of cases seen early is small.

In 1920 Taussig⁵⁶ emphasized the requirements necessary for the successful irradiation of gynecological carcinomata and stressed the now generally accepted view that these treatments should be given only by an experienced gynecologist.

The necessity for an accurate diagnosis not only as to the character of the tumor but its extent, which in most

instances is dependent upon bimanual examination, can only be determined by one thoroughly familiar with this method of diagnosis. Graves has pointed out the dangers of ill-advised irradiation.

SARCOMA OF THE CERVIX.—Sarcoma of the cervix is a rare disease. Our experience is limited to four cases all of which followed supravaginal hysterectomy for supposed myomata. Hurden⁵⁷ divides sarcoma of the cervix according to its morphology into two groups, (a) an indefinite group comprising the ordinary varieties of sarcoma and (b) racemose myxosarcoma. The tumor may be secondary to a sarcoma of the body of the uterus, or sarcomatous degeneration of a myoma, or may be primary in the cervix. Occasionally cervical myomata undergo sarcomatous degeneration. Gessner⁵⁸ found the tumor situated in the cervix in 12 per cent. of uterine sarcomata. Meyer⁵⁹ found the tumor in the cervix in 3.3 per cent. of sarcomata and Piquand⁶⁰ in 17.5 per cent. of cases. The tumors are often polypoid, sometimes interstitial or diffuse, single or multiple. The macroscopic appearance depends upon the type of sarcoma; some possess a moderately thick capsule whereas in others, notably the unripe type, the capsule is thin and inconspicuous.

Likewise the cut section is variable in appearance, the spindle-cell varieties being moderately firm and fibrinous whereas the round-cell type are smooth, vascular, homogeneous, whitish or pinkish in color and quite soft and friable. In its early stages the surface is smooth and covered with cervical epithelium. On cut section the sarcomatous tissue can often be seen penetrating in an irregular manner the surrounding structures. The circumscribed tumors resemble myomata. The diffuse variety is distinctly infiltrating even on gross examination. In the diffuse forms the mucosa may

be uniformly invaded, generally the vaginal cervix exhibits the more extensive involvement. The cervix may be uniformly enlarged but more commonly a distinct nodule is observed with irregular vascular papillomata upon the surface. The tumor tends to break down later than does cancer, for which, however, it is frequently mistaken. The lobulated, polypoid variety is the most frequent form encountered.

Histologically, round-cell, spindle-cell, giant-cell and mixed types have been most frequently described. Melanosarcoma (metastatic), alveolar and angiosarcoma have also been observed. The tumors are probably of myogenic origin. Sarcoma of the cervix is frequently mistaken for carcinoma, myoma or polypi and the correct diagnosis only arrived at upon histologic examination. Ewing⁶¹ states that metastasis appears late with the encapsulated interstitial tumors, but when the parametrium is invaded, secondary growths often appear in the regional areas and in the lungs as well as elsewhere. Those tumors containing chiefly round or giant cells are the most rapid in growth, give earliest metastasis and are in general the most malignant. The histologic structure of the round-cell variety is often mistaken for an endothelioma.

The so-called racemose myxosarcoma is a similar growth to that occurring in the vagina of infants and children (see chapter on Malignant Tumors of the Vagina). As stated, cervical sarcoma is an infrequent neoplasm and a sufficient number have not been treated and recorded to judge the effects of irradiation. The unripe types are doubtless susceptible to irradiation. A high trachelectomy performed with the cautery and the irradiation of the stump as described under the treatment for cervical carcinoma would be our method of choice when involvement of the body of the uterus

was not present; in the latter event hysterectomy followed by deep X-ray would probably give the best results.

ENDOTHELIOMA. — This is a rare tumor. Some authorities question its existence. The more carefully such tumors are examined the fewer true endothelioma are found and the greater number of sarcomata. In 1916 Dorland ⁶² reviewed the literature on this subject. Of 30 endotheliomata 16 were cervical. The tumors, clinically, resemble sarcomata. We have no experience with the treatment of endotheliomata of the cervix. We would, however, recommend the same treatment for this tumor as for sarcomata.

EPIDERMOID CARCINOMA OF THE CERVIX TREATED BY CAUTERY AMPUTATION AND RADIUM. — The patient was a white woman 42 years of age. Has had the diseases of childhood but with the exception of pneumonia 12 years ago has never had any serious previous illness.

The patient was married at 22 and has had four children, the last eight years ago. All the labors were easy, one miscarriage six months after marriage at the fourth month due to a fall. Leukorrhea has been present in a moderate amount since the birth of the second child. This has never been sufficient to require the wearing of a pad, it has been most marked for the few days following the cessation of the menses.

Menstruation began at 14, was of the five-day type; there was considerable dysmenorrhea before marriage. This became markedly less after the birth of the first child and has never been severe since. The flow is moderately profuse on the second and third days of the period requiring the use of four or five pads. During the fourth and fifth days of the period the flow is much less.

Development of present trouble. About three months ago the patient noticed a few spots of blood on the bed

clothes following coitus, a week or two later a few spots were observed upon the clothing and since then the bleeding has increased in frequency and amount. The blood is bright red. It frequently follows strain at stool, coitus, slight jars or jolts and sometimes comes on without apparent cause. The bleeding has never been severe enough to cause alarm until a week ago when there was a rather sharp hemorrhage lasting for an hour or two during which time she soaked three pads. She then visited her physician who immediately referred the case. There has been no noticeable increase in the leukorrhea, nor has this been of a foul odor. There has never been any pain, no loss of weight or other symptoms. On admission to the hospital the preceding history was secured.

Physical examination showed a large well nourished apparently healthy woman. Heart and lungs were normal. Urinalysis showed normal urine. Hemaglobin was 85, R.B.C. 4,100,000, W.B.C. 4600. Systolic blood pressure 130, diastolic 90. Weight, 150 pounds.

Abdominal examination was negative.

Pelvic examination showed the external genitalia normal, a moderate sized rectocele was present. The cervix was perhaps slightly hypertrophied, it could be pulled down almost to the introitus and presented a moderately deep bilateral laceration. An area of erosion 1.5 cm. in diameter surrounds the external os. Situated upon the posterior lip and involving to a lesser extent the anterior lip was an ulcer, bright red, hard to the touch, the floor of which was covered by a greenish black slough. This ulcer bled easily upon slight touch and upon close inspection could be differentiated from the previously described area of eversion upon which it was situated. The cervix was freely movable, there was no indu-

ration or thickening of either broad ligament. The fundus was normal in size, consistency, position and mobility. The right adnexa was not palpable. There was no tenderness even on deep palpation. The left ovary was felt as an oval almond-shaped organ and apparently normal.

Examination per rectum yielded no further information.

Proctoscopic examination showed a normal rectum.

Cystoscopic examination showed a normal bladder.

DIAGNOSIS.—Carcinoma of the cervix, stage i, ulcerative in type, laceration of the cervix with eversion, rectocele, and remainder of pelvic organs normal.

RECOMMENDATION.—Trachelectomy with the cautery and irradiation.

Patient was prepared for operation in the usual manner.

OPERATION.—Nitrous oxide gas anesthesia. The cervix was pulled down, care being exercised not to traumatize the carcinoma. The bladder was freed from its uterine attachment nearly to the peritoneum. A number 2 catgut suture mounted upon a round pointed Mayo needle was passed through the cervix on each side at about the cervico-uterine junction. These were tied and answered the double purpose of checking hemorrhage and acting as tractors. With the cautery knife bent at an obtuse angle the cervix was slowly amputated in a circular manner just below the catgut ligatures. During the amputation the cervical canal was coned out so that the lever of the amputation was much higher at the canal than at the periphery of the cervix. After the amputation 50 mg. of radium were inserted into the remains of the cervical canal and lower uterine cavity and stitched in place. Another 50 mg. of radium was placed transversely in the coned out stump and held in place by a stitch. The patient was catheterized. Two large Sims speculæ were

inserted and the anterior and posterior vaginal walls, bladder and rectum packed far back out of the field of irradiation. This was especially easy to do as the bladder had been widely freed from its uterine attachment before commencing the actual trachelectomy. The speculæ were withdrawn. A vulvar pad held in place by a T-bandage was applied.

CONVALESCENCE.—The patient was catheterized twice at six-hour intervals after which time she voided. The vaginal gauze pack and radium were removed at the end of 24 hours. The patient was allowed out of bed on the eighth day and returned to her home on the eleventh day. Convalescence was normal. Three weeks after the operation there was little local reaction and under light nitrous oxide gas anesthesia 2000 mg.h. of radium was administered by needles placed in the periphery of the cervix. Convalescence from this was normal. No further irradiation was given nor was the X-ray employed. The cervical wound gradually healed. At first there was considerable discharge. This slowly diminished and finally ceased.

Examinations were made at monthly intervals for the first six months, and from then on every eight or ten weeks, no evidence of recurrence appeared. The patient has been under observation six and one-half years.

Histologic examination showed an ulcerative epidermoid (basal-celled) cervical carcinoma. This involved the portio and extended upwards along the cervical canal to the point of amputation. A moderately wide zone of healthy tissue surrounded the carcinoma both laterally and upon the anterior and posterior surface.

COMMENT.—Although this was apparently an early carcinoma it had already extended upwards along the cervical canal to at least the level of amputation and perhaps

above. The freeing of the bladder permitted a trachelectomy at a high level which was further facilitated by the mobility of the uterus and laxness of the uterosacral ligaments. The trachelectomy undoubtedly aided in the accurate application of the radium. The rectocele was of moderate degree but was not repaired because of the shrinkage of the vagina which was sure to follow the heavy irradiation. This patient suffered quite severe menopausal symptoms for the year following the operation which were not relieved by either corpus luteum nor whole ovary extract given both by mouth and hypodermic.

RECURRENT CARCINOMA OF THE CERVIX TREATED BY IRRADIATION.—Patient was a white female, age 50 years, married.

FAMILY HISTORY.—Father died of nephritis and her mother of diabetes; no history of tuberculosis or malignancy.

PAST HISTORY.—Patient had the usual diseases of childhood but no serious illnesses. Menstruation was established at 15, regular, 28-day interval, four to five days in duration. It was normal in amount and character. She was married at the age of 21 and has had six children; all normal deliveries. Two of these children died in infancy; four are living and well. Four years before her admission to the hospital, or in July, 1921, she had moderate bleeding twice in four weeks. This alarmed her and the patient immediately consulted a physician who told her she had a cancer and must be operated on immediately. She was admitted to another hospital and a panhysterectomy and bilateral salpingo-oöphorectomy were performed. An uneventful recovery followed the patient leaving the hospital three weeks later. Her general health was good and she was not ill at any time following the operation. The patient was referred to the Radiological

Department of the Philadelphia General Hospital and made regular visits to the follow-up clinics. In February, 1925, or seven months after the hysterectomy a small ulcerated lesion was noticed in the vault of the vagina. This presented the usual characteristics of a recurrence. The ulcer was 1 cm. in diameter. This was treated under nitrous oxide anesthesia with radium seeds and radium, the total dosage amounting to 2400 mg.h. Histologic examination of the tissue obtained at the time of treatment showed a squamous-celled carcinoma. Cystoscopic and pelvic examination at this time failed to reveal other evidence of recurrence. Two months later there was a shallow, necrotic indolent ulcer at the site of the irradiation which did not bleed on touch. There was no further evidence of recurrence. On April 25th, under nitrous oxide gas anesthesia a second irradiation was applied, 12 bare tubes approximating a total dosage of 1124 mg.h. were implanted in and around the edges of the ulcer. A biopsy at this time showed necrotic tissue and areas of squamous-celled carcinoma. Recovery was normal. The patient was observed at monthly intervals. She showed a moderate local radium reaction which gradually cleared up. Between June 6th and July 7th, 1926, the patient had six deep X-ray treatments, three anteriorly and three posteriorly. There was practically no reaction from this treatment. There was never any further evidence of recurrence, and in April, 1927, there was no bleeding, no discharge, and no other evidence of recurrence. Complete local healing had occurred. There were no symptoms of any kind and patient feels absolutely well.

COMMENT.—This was a local recurrence probably due to failure to remove a sufficiently wide cuff of vaginal mucosa at the time of the hysterectomy. Whereas, the patient is by

no means safe from further recurrences, at worst her life has been prolonged and made more comfortable and there is a definite chance of a permanent cure as two years have passed since the first irradiation and the patient is still in apparent perfect health.

CASE OF STAGE IV CARCINOMA OF THE CERVIX ASSOCIATED WITH A SMALL UTERINE MYOMA, TREATED FOR PALLIATIVE PURPOSES ONLY.—The patient was a white female, age 36, married.

FAMILY HISTORY.—Practically negative. Her father and mother are living and well and no history of tuberculosis or neoplasms is present.

PAST HISTORY.—The patient had measles and mumps as a child, and influenza during the epidemic. Menstruation was established at 14, regular, 29-day interval, five days in duration, normal in amount and character with very little dysmenorrhea. Five children are living and well. All the labors were normal.

PRESENT ILLNESS.—Two years prior to her admission to the hospital, the patient developed a mild metrorrhagia and irregularity with intermenstrual bleeding which increased in severity until one year ago when the flow moderated slightly for a short time. The five-day duration period increased to seven and then to nine and the metrorrhagia became more marked. For the past eight or nine months, the bleeding has been nearly continuous and at times extremely profuse so that all record of normal periodicity has been lost. She is losing ground rapidly, because of the continuous hemorrhages. In July, the patient was admitted to the Radiologic Department of the Philadelphia General Hospital. Bleeding was the chief symptom; she was using 8 to 12 and occasionally 14 napkins daily. There was marked dysuria and pain

involving the entire pelvis and lower abdomen. There had been a considerable loss of weight.

Physical examination showed tonsillitis, pyorrhea and numerous dental cavities. The heart was rapid and the sounds of poor quality. No murmurs were present. The lungs were normal. The systolic blood pressure was 98 and the diastolic 68.

Abdominal examination showed no abnormalities except tenderness on deep palpation in both ovarian regions.

PELVIC EXAMINATION.—The external genitalia are normal. The vagina is multiparous but there is good support. The rectovaginal and vesicovaginal septa are thickened and infiltrated, a profuse, thick, blood-stained mucopurulent, malodorous leukorrhea is present. The place of the cervix is taken by a hard indurated, fixed, ulcerated neoplastic mass which measures 6 cm. in diameter. This bleeds freely on touch and presents the usual appearance of an advanced cervical carcinoma. The fundus is enlarged, nodulous and adherent. The parametria are thickened and board-like.

Urinalysis (per catheter specimen) showed a cloud of albumen but was otherwise negative. Hemoglobin was 52 per cent. The Wassermann test was negative.

DIAGNOSIS.—Carcinoma of the cervix, stage iv associated with a uterine myoma. Prognosis hopeless.

TREATMENT.—Owing to the character and location of the tumor it is possible to apply radium without danger of producing a fistula and with a definite hope of checking hemorrhage. It is believed that much of the pain from which this patient suffers is due to the cellulitis and doubtless to an extent also to extension to the broad ligaments. If the ulcer can be cleared up it is hoped the cellulitis will be reduced and pain lessened. For these reasons irradiation is advised as a

palliative measure. Twenty-four hundred milligram hours of radium was administered in the usual manner, 1200 mg.h. in the canal and 1200 mg.h. against the face of the tumor. Biopsy showed a squamous-celled carcinoma. This treatment did not entirely check the hemorrhage, although for a time the bleeding was lessened. Two months after the irradiation the bleeding was again profuse requiring 10, 12 or 14 pads daily. The hemoglobin was 30 per cent. and the patient was weak and confined to bed. A second irradiation was decided upon. Under light nitrous oxide anesthesia 100 mc. of radium was buried in the centre of the neoplasm, and remained in place for 12 hours. Convalescence was normal. The biopsy performed at the second irradiation showed a squamous cell carcinoma exhibiting evidence of previous irradiation.

One month after the second irradiation all bleeding had ceased and did not recur. There was a moderate amount of mucopurulent discharge. Two months after the second irradiation there was a marked improvement, the hemoglobin was 60 per cent. and the patient was able to be about for four or five hours a day mostly in a wheeled chair. There is little change in the intraperitoneal lesions. The vaginal surface shows a moderate radiation reaction but is markedly less friable than formerly. From this time on until six months after the second irradiation there was improvement, from the third month after the second treatment the patient was able to spend most of her time out of bed. There was little discharge, a steady rise in the hemoglobin and decrease in the symptoms incident to the anemia. During the seventh month the patient grew steadily weaker and during the eighth month died from uremia evidently due to pressure upon the ureters by the carcinoma. There was never much pain after the second treatment and that which was present

was controlled for the most part by codeine or small doses of morphine.

COMMENT.—This was an advanced cervical carcinoma. Life was undoubtedly prolonged four to six months by the treatment. This in itself may be of secondary importance if the patient is suffering acutely. The treatment undoubtedly improved the cellulitis and as a result pain was markedly lessened and indeed after the second treatment until the time of death was almost eradicated and for this reason the irradiation appears to have been justified.

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CHAPTER VII

MALIGNANT TUMORS OF THE BODY OF THE UTERUS

CARCINOMA of the body of the uterus is the most frequent malignant neoplasm occurring in this area. It constitutes almost 15 per cent. of all cancers of the female genital tract and about 20 to 25 per cent. of all uterine carcinomata. It is an established fact that chronic irritation is a predisposing factor towards carcinoma. Cervicitis, especially in cervici which have been the seat of laceration, is extremely frequent, whereas true, chronic corporeal endometritis is infrequent, and if we exclude the tuberculous variety, quite rare. It is probable that these facts have a definite bearing upon the lesser frequency of fundal than of cervical carcinomata. The combination of tuberculous endometritis and cancer have been recorded by a number of observers. (D'Holluin and Dalral¹ and Norris.²)

In a series of 115 cases of fundal carcinoma recently reviewed by Norris and Vogt³ the average age was 53 years; Peterson states that 73 per cent. of his cases were between 55 and 65 years of age. All large series show that the disease occurs somewhat later than does cervical cancer. (Koblank⁴ and Cullen.⁵)

Cancer of the fundus is relatively frequent in spinsters; 26 per cent. of our series occurred in unmarried women. Like cervical carcinoma, the chief symptoms of value in the early stage are hemorrhage and discharge. Because of its protected location and histologic character, discharge is of somewhat greater importance as a diagnostic sign than in the

cervical tumor. The hemorrhage is of the same irregular character, consisting of bright blood, generally small in quantity in the early stages, is progressive in character and is prone to follow trauma. The tumor, however, not being so subject to direct trauma, this is less pronounced. Hemorrhage often occurs after straining at stool or a vigorous bimanual examination. The discharge, owing to the glandu-

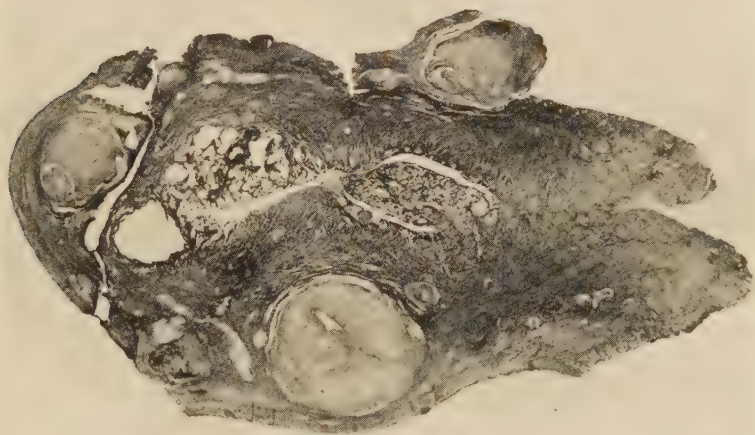


FIG. 45.—Carcinoma of the fundus, small multiple myoma and an endometrial polyp. Actual size except for shrinkage due to fixation.

lar character of the tumor, is more pronounced than in cervical cancer and is thin, malodorous and irritating.

In 65 per cent. of our cases the uterus was normal in size so that enlargement of the uterus while suggestive when present, is of little value as a negative sign. Early diagnosis is of the utmost importance. In our entire series, 34.8 per cent. were alive at the end of three years and similar results are recorded by the majority of carefully controlled studies by others. This is in contradistinction to the rather popular

belief that carcinoma of the fundus is a relatively favorable type of disease. The integrity of the myometrium is the most important prognostic sign.

When the disease develops after the establishment of the menopause, a tentative diagnosis is not difficult. Hemorrhage occurring after this period is more like to be due to cancer than to any other cause. Prior to the menopause so many other conditions may be present which are likely to result in hemorrhage that the determination of the cause is less easy. To the experienced physician the symptoms previously described are always suspicious and the condition is very properly viewed as malignant until found otherwise. This proof, however, is not always easy to secure. The ordinary pelvic examination is often entirely negative and this in itself is suggestive of fundal carcinoma. The curette, of course, offers a practically certain means of diagnosis. Curettage is not, however, in the ordinary sense, an office procedure and for this reason occasionally cases are allowed to advance under treatment by uterine styptics or other forms of medication.

The test suggested by Clark, while less certain than curettage, is of great practical value. It is applicable to all suspicious cases and may be safely employed in the office and has the additional advantage of requiring no special apparatus or histologic knowledge. It consists in cleansing the external genitalia, vagina and cervix thoroughly with an antiseptic solution and then passing under sight a sterile sound to the fundus of the uterus and gently manipulating the point of the instrument over the entire endometrial cavity. If a friable, vascular growth, such as a carcinoma is present, a small trickle of blood will be observed. In employing this test it is best not to grasp the cervix with a tenaculum. It is



Fig. 46. -Adenocarcinoma of the fundus and small myomata. Diagnostic curetage and irradiation (3000 mg./h.) followed by hysterectomy. No recurrence three and a half years later.

possible that other pathologic conditions may cause bleeding from this test; the non-appearance of blood from the cervix indicates strongly that no cancer is present.

That the clinical diagnosis is not always easy is shown by the fact that in our series it was positive in but 57 per cent. of cases and suspected in an additional 23 per cent. In 19 per cent. the cancer was unsuspected. An interesting feature brought out by this study was that in 75 per cent. of the unsuspected cases the symptoms of the carcinoma were masked by those produced by a preëxisting uterine myoma.

One of the writers⁶ has elsewhere drawn attention to the limits of microscopic diagnosis. Occasionally doubtful histologic pictures will be observed which will be interpreted differently by the most experienced pathologists. As a general rule doubtful specimens are benign. If the curettage has been a thorough one there is rarely room for doubt in the class of cases under discussion. Occasionally a fundal cancer may be protected from the curette by an obstructing submucous myoma, or uterine malformation but such instances are rare and the diagnosis by curettage can be depended upon in practically 100 per cent. of cases. Sampson⁷ has referred to the possibilities of transtubal implants of carcinoma cells following curettage. We have on two occasions demonstrated undoubted cancer cells lying free in the tubal lumen and have elsewhere reported a case that appeared to be an undoubted ovarian implantation following curettage. We believe that transtubal dissemination accounts for many of the cases of combined ovarian and fundal carcinoma.

Despite the possibilities of transtubal implants following curettage, this operation is indispensable in a proportion of cases and were it eliminated as a diagnostic aid it would mean either sacrificing many normal uteri or allowing many

early fundal cancers to become advanced. The risk incurred by the operation is far less than that which results from any other method of treatment. The possibilities of transtubal implantation of carcinomatous cells should, however, be borne in mind. The dilatation should be a thorough one; irrigation is inadvisable and the packing of the uterine cavity or forcing through the cervical canal radium-bearing rubber tubes, etc., which may act as a piston should be avoided. In the subsequent hysterectomy the tubes should be tied off near their distal extremity as a preliminary step to removal of the uterus. The hysterectomy itself should be performed without delay. Radium irradiation at the time of the diagnostic curettage is advisable and likely to destroy loosened cancer cells. These precautions should materially lessen the risk of transtubal metastasis.

For treatment in the cases in which the diagnosis is in doubt we prefer to do a curettage and safeguard the operation against transtubal metastasis as above described. We employ a rapid paraffin method which ensures satisfactory histologic preparation in 16 hours. This permits the hysterectomy to be performed on the day following the curettage if so desired. If the diagnosis is moderately certain or other intrapelvic lesions exist, such as myomata, hysterectomy without a preliminary curettage is the method of choice.

Fundal cancer is by no means an especially embryonal type of neoplasm and irradiation doses should be about twice that given to a basal-celled cervical cancer, 5000 to 7000 mg.h. being none too much. The cancer can generally be located with moderate accuracy with the curette and the radium placed directly in this area. Our follow-up has shown that the best results have been secured in those cases which had a preliminary intrauterine irradiation, although the

dosage has usually been small, about 2400 mg.h. Our series showed the following results:

Hysterectomies only or D. & C. immediately followed by hysterectomy:

Number of cases 35

Percentage alive three years or more later . . 37.5 per cent.

Hysterectomies preceded by 24 or more hours by D. & C. and 2400 mg.h. radium irradiation:

Number of cases 22

Percentage alive three years or more later . . 40.9 per cent.

The more favorable results in the latter group may be accounted for by either the fact that cases in which a diagnostic curettage is necessary are as a rule earlier cases or that the irradiation was the beneficial factor; probably both aided in securing the results. In our series there were ten cases which for various reasons were treated by D. & C. and irradiation only; of these 50 per cent. were alive at the end of three years. With two exceptions these cases were treated by a single application of 2400 mg.h. One case occurred in a woman weighing 320 pounds and who had decompensation and nephritis. The uterus was enlarged and the entire top of the fundus and one side of the endometrial cavity appeared involved. She was given three applications of 2400 mg.h. each at three-week intervals. This patient was examined three and a half years later and exhibited no evidence of recurrence.

We believe this latter group too small from which to draw conclusions. Where definite contraindications to hysterectomy exist radium may well be employed and is advisable for the reasons indicated in conjunction with diagnostic curettage.

Carcinoma of the fundus occurs but rarely in young

women and if the histologic examination of the curettings prove them benign no harm and probably benefit has accrued from the irradiation. Bailey and Healy⁸ record unsatisfactory results from the use of radium in fundal cancers. They state that in nearly every instance cases subjected to irradiation only, exhibited evidence of recurrence within one year. Philipp and Gornick⁹ report 40 operable cases treated with radium from which they secured 45 per cent. of five-year cures.

For the reasons stated in the chapter on cervical cancers, we have not emphasized postoperative irradiation nor has postoperative X-ray been employed at the University Hospital except in a few cases. In the service of one of the authors at the Philadelphia General Hospital, postoperative, deep X-ray therapy has been utilized routinely. The time is yet too short and the number of cases too small from which to draw conclusions. Many of the foreign clinics use deep X-ray therapy routinely in these cases as a postoperative treatment.

CHORIONEPITHELIOMA.—The time is yet unripe for any positive statement regarding the merits of irradiation for this tumor. Based upon its histologic structure it would seem that the neoplasm should be susceptible to irradiation. Special care should, however, be exercised in drawing conclusions regarding the comparative merits of this procedure, especially from individual or small groups of cases. This tumor varies greatly in malignancy; many efforts have been made to correlate its histologic structure with its degree of malignancy. The tumor is by no means a frequent one and for this reason many pathologists have not had the opportunity of studying large series of specimens. At best the histologic diagnosis from fragments of the tumor is often difficult and in some instances impossible.

In the case of curettings and without knowledge that an actual neoplasm is present, this is especially the case. It is probable that many uteri have been sacrificed as a result of an incorrect histologic diagnosis, and these cases, if they survive the operation, go to swell the list of cures. Ewing¹⁰



FIG. 47.—Chorio-epithelioma. Diagnosis from curettings, panhysterectomy. Recurrence and death. Postmortem showed widespread metastases involving lung, liver, spleen, kidney and bones.

divides these tumors into three types which may be distinguished by gross and microscopic structure, and states that between these there are transitional cases: (1) chorio-adenodestruens, destructive placental mole; (2) chorio-carcinoma; (3) syncytioma and syncytial endometritis. The same authority states that chorio-adenoma regularly follows hydatid mole and occurs usually in multiparas over 40 years of age. Hemorrhage is the first symptom. Curtis

and Ovi¹¹ record recovery in 11 of 14 cases treated by hysterectomy, and three deaths. Manual extraction of the mole and curettage were successful in two cases reported by Herz¹² and one patient subsequently gave birth to a healthy child.

Choriocarcinoma may follow normal labor, hydatid mole, ectopic pregnancy and abortion at varying intervals. Hemorrhage is the chief symptom but may not be as marked as in the former variety. The uterus is often only slightly enlarged; all uterine symptoms may be absent and distant or nearby metastasis the first evidence to call attention to the condition. Regardless of whether hysterectomy is performed, death generally results in 18 months at most. We have observed widespread metastasis and death within ten weeks and Schlagenhauer¹³ has recorded a similar case in 34 days.

Ewing states that he has been unable to find any record of an operative cure. Widespread metastasis occurs early and subsequently operation only hastens the end. Owing to the intravascular and friable character of the tumor the danger of trauma metastasis is very great.

Syncytioma or syncytial endometritis may follow abortion, hydatid mole or placental polyp, but a definite history of such is often lacking. Irregular and profuse bleeding is the chief symptom. The uterus is enlarged and curettage yields masses of necrotic material. Many cases recover after this operation and Mange recommended it as the operation of choice. Teacher¹⁴ reported 188 cases with 65 recoveries: some of these doubtless subsequently suffered recurrence.

As will be observed, choriocarcinoma is the most malignant variety and although recoveries doubtless occur after early operation, such cases are rare, and the tumor extremely

malignant. Our experience coincides with that of Ewing above quoted. Some cases are easily grouped under the Ewing classification; quite a few, however, appeared to us to have been intermediate types and varied in their histologic characters quite markedly in different portions of the tumor. This inability to classify may be due to inexperience. As will be seen, the tumor varies from an extremely high degree of malignancy to one often cured by curettage or other evidently incomplete operation. Rockafellow reported a case operated upon four times for recurrences; the patient's condition became so bad that it did not seem justifiable to attempt further removal. To everyone's surprise, the growth began to shrink and ten years later the patient had gained 62 pounds and seemed in perfect health. The end-result of the case is recorded by Lynch and Maxwell.¹⁵

Many isolated reports of remarkable recurrences are present in the literature. Because the tumor is infrequent and owing to its variable malignancy and difficulty of classification as to its grouping unless examined by an experienced pathologist, it is difficult to estimate the relative value of the different treatments. It is unsafe to draw conclusions from isolated cases for, as shown, these may recover even though incompletely removed. Because of its embryonal character it would seem that the tumor should be susceptible to radium and X-ray.

The authors have had one case of recovery following incomplete operation and radium irradiation and many others have been recorded. Whether to attribute such cases to lack of malignancy of the tumor, as those cases which recover after incomplete operation, or to view the result as due to some reaction developed in the body by the influence of the irradiation, it is impossible to determine. The results

following hysterectomy for the definitely identified choriocarcinoma are extremely unsatisfactory, whereas the value of irradiation is still unproven.

SARCOMA OF THE BODY OF THE UTERUS.—In the Gynecological Laboratory of the University of Pennsylvania we have found 39 sarcomata of which four were cervical among 11,416 specimens. Veit¹⁶ found the proportion of sarcoma and carcinoma to be 1-37.2 and Evans¹⁷ 1-40. From some clinics sarcoma has been reported much more frequently, probably due to the fact that degenerating or cellular myomata have been classified as sarcomata. Sarcoma of the body of the uterus in our series was about four times as frequent as in the cervix. Many authorities place the proportion considerably higher. Gessner,¹⁸ 8-1, and Meyer,¹⁹ 29-1. The tumors are probably of myogenic origin.

Sarcoma may originate as a mural tumor or from the stroma of the mucosa (Virchow), the former being the more common, especially in the body of the uterus. The mural tumors may occur as primary neoplasms or may develop secondarily in myomata. In either case they more or less resemble myomata. They are prone to be softer, more vascular and homogeneous. Areas can often be detected macroscopically in which the tumor is invading the capsule. The gross appearance depends largely upon the histologic type of tumor present. The round-celled varieties being more opaque, homogeneous and less fibrous and can generally be identified by the naked eye, whereas the spindle-celled types are usually recognized only upon microscopic examination. Hemorrhage and liquefaction necrosis is common.

The sarcoma springing from the endometrium may be polypoid or diffuse and intermediate types are often observed. These varieties may attain considerable size, the

uterus becoming enlarged and the myometrium altered and often thinned out or hypertrophied.

Pyometra and hematometra sometimes develop. Invasion of the myometrium and involvement of the cervix is frequent. In the polypoid type tumor masses may project from the cervical canal. Sarcoma of the uterus may be spindle-cell, round-cell or giant-cell forms, or combinations of these types may occur. Various more minute classifications have been suggested. In some tumors decidual-like cells are present. These have been attributed by Myer to changes incident to menstruation. The unripe varieties give early and often distant metastasis and tend to recur, whereas the spindle-cell types are less malignant. As in fundal carcinoma, the integrity of the myometrium is the most important prognostic sign. Those tumors which are definitely encapsulated, as in the case of early sarcomatous degeneration of myoma, are the most favorable. Prior to operation the mural varieties are often mistaken for myomata although the rapidity of growth is often suggestive.

TREATMENT.—Each case should be judged individually. As a general rule, panhysterectomy is the operation of choice, followed, especially in the more unripe types, by deep X-ray therapy. In case a diagnostic curettage is performed, intrauterine irradiation at the time of the curettage is advisable, employing the precautions against transtubal metastasis described under the heading of fundal carcinoma.

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CHAPTER VIII

MYOMA OF THE UTERI AND MYOPATHIC HEMORRHAGE

FIBROMYOMATA of the uterus are frequently referred to as fibroids or myomata and are the most frequent of all gynecologic neoplasms. Myomata are present in from 4.3 per cent. (Moller¹) to 20 per cent. (Kelly and Cullen²) of all gynecologic patients. Many small, symptomless myomata are never recognized. In those statistics formulated largely from colored patients, the proportion of myomata is always high. Combined statistics of Frank,³ Kelly and Cullen⁴ and McDonald⁵ formulated from 2391 cases show that 70 per cent. of patients are between 35 and 50 years of age.

These figures represent the age at which the patient sought relief. As the tumors are slow-growing, the age at which they developed was obviously considerably younger. Myomata are relatively infrequent under 30 and rarely require treatment after 55 years of age.

All myomata have their origin in the myometrium and from this site may develop inwards and become submucous and even pedunculated, or outwards, subperitoneal or intraligamentous. The subperitoneal variety frequently become pedunculated, and eventually the pedicle may become attenuated or entirely disappear and the tumor become parasitic or wandering, and receive all its nourishment through adhesions from the omentum or adjacent structures; in rare instances the intraligamentous variety may in the same manner become separated from the uterus. Uterine myomata are usually multiple, tumors of varying sizes being present.

Whether this is due to tumors in certain portions receiving more nourishing and a richer blood supply and hence growing more rapidly, or to a continuance of the stimulus which leads to the development of the neoplasms over a long period, resulting in the appearance of successive crops of myomata, is unknown.

The latter would appear the more likely explanation. The submucous type is the variety most prone to be single. Myomata form irregular nodular neoplastic masses, varying in size up to huge tumors reaching to the diaphragm. The tumors are of slow growth and generally cease to increase in size and may actually shrink after the menopause, but as the menopause is often greatly delayed, this characteristic is of little value to the patient suffering from one of these tumors. The tumors are composed of unstriped muscles and fibrous tissue in varying proportions. The capsule is probably derived from the myometrium and as the neoplasm pushes outwards or inwards the capsule becomes thinned out so that eventually it may be quite thin. The capsule carries the blood-vessels supplying the tumor which is often quite avascular, especially towards the centre.

The symptoms produced by myomata are too well known to require description. Hemorrhage and pressure symptoms and symptoms developing from complications such as salpingitis are among the most frequent. The character and severity of the symptoms are in accord with the lesions present, and as these vary greatly so also do the symptoms. All cases are symptomless in the early stage and some never cause trouble. It is difficult to estimate the rate of growth. We have seen many cases in which the tumor remained *in statu quo* for many years and this in women prior to the menopause. Kelly and Cullen⁶ mention cases in which the

tumor has been known to have been present and of large size for 22 years. On the other hand we have seen tumors develop relatively rapidly. As a rule pedunculated tumors and tumors of great size grow more slowly. Myomata generally cease to increase in size after the establishment of the menopause.

The menopause is, however, usually delayed. After 50 years of age the tumors are more likely to be of slow growth. Rapid enlargement is suggestive of malignancy and of a mistaken diagnosis. Under the influence of pregnancy myomata generally exhibit a more rapid increase in size and are prone to shrink somewhat during the involution of the uterus following gestation.

Tumors which cause pressure upon the endometrium are most prone to be productive of hemorrhage. The hemorrhage nearly always begins as a menorrhagia. The menorrhagia increases in duration until in some cases the bleeding is almost constant; in others the flow becomes irregular. There is, however, in the hemorrhage produced by myomata a definite tendency towards periodicity, in contradistinction to the hemorrhage of cancer, which is irregular and metrorrhagic in type. As a result of hemorrhage, various symptoms incident to the anemia are likely to develop and are frequently prominent features. In many cases hemorrhage is the only symptom. Hemorrhage has been the most pronounced or only symptom in about 40 per cent. of the cases applying to the University Hospital for treatment. Pressure symptoms have been more or less marked in 34 per cent. of our cases.

In an analysis of 934 cases Kelly and Cullen⁷ found inflammatory lesion of the tubes present in 45 per cent. of cases. In our own material an inflammatory lesion was present in one or both adnexa in 52 per cent. of cases submitted to hysteromyomectomy. About one-third of our

cases have been treated by irradiation and it is presumed that in these the adnexa were normal. Inflammatory lesions are more frequent among negroes and in clinics having a large proportion of these patients the incident of salpingitis is higher.

The diagnosis of uterine myomata is usually not difficult, but the recognition of complications, many of which may be contraindications to irradiation, is often not so easy. An accurate and complete diagnosis is of much more importance if the tumor is to be treated by irradiation than if an abdominal section is to be performed; in the latter case an adnexa, the seat of an inflammatory lesion or the presence of a small ovarian neoplasm does not greatly alter the ultimate outcome, whereas if irradiation is to be performed either of these complications may cause a fatal termination.

In a previous chapter we have dealt somewhat in detail upon the theories which have been advanced to explain the beneficial action of radium upon uterine myomata. To briefly recapitulate, these are: (a) action upon the ovary and destruction of its follicle-bearing constituents, (b) the production of an endarteritis of the blood-vessels of the tumor and myometrium, (c) the increase in amount of fibrous tissue in the neoplasm and myometrium, and (d) the formation of cicatricial tissue in the endometrium. For reasons previously stated, we place the greatest reliance in the theory first mentioned. Doubtless, however, the production of an obliterative endarteritis is a contributing factor. The increase in amount of fibrous tissue is difficult to prove as the proportion of this tissue varies markedly in uteri which have not been subjected to irradiation.

We place little credence upon the theory of cicatricial tissue formation in the endometrium. We have examined

numerous uteri which have been irradiated and have rarely been able to demonstrate scar tissue except in recent cases. It is necessary to understand the manner in which radium acts in order to make a proper selection of cases suitable for irradiation. In the treatment of these cases, irradiation should be the hand-maiden to and not the competitor of surgery.

As far as treatment is concerned, uterine myomata can be divided into three groups: (a) the small, uncomplicated, slow-growing or stationary, symptomless myomata which do not ordinarily require any treatment other than periodic observation, (b) tumors which are best treated by myomectomy, or hysteromyomectomy, according to the individual case, and (c) cases suitable for irradiation.

Many cases belong to the first group, the majority to the second and about 25 or 30 per cent. to the third. Perhaps the easiest way to express our views regarding irradiation is by a process of exclusion and to state primarily the contraindications to irradiation.

The indications and contraindications to irradiation will be better understood if we consider the limitations of irradiation. Irradiation may be expected to check uterine bleeding resulting from myomata in practically all cases in which an adequate dosage is employed. Tumor shrinkage or even entire disappearance of the neoplasm as far as palpable findings are concerned may also be expected in the majority of cases. This result is not, however, so certain as is the development of amenorrhea. Furthermore, the shrinkage is usually a slow process involving months and sometimes years. With these facts in mind the following contraindications to use of irradiation are easily explainable. Certain exceptions to these rules may occur:

1. Cases in which doubt exists as to the accuracy of diagnosis.
2. The presence of intraperitoneal lesions other than the myomata which require surgical intervention.
3. Rapid growth.
4. Associated neoplasms such as fundal carcinoma or ovarian tumor.
5. Pressure symptoms.
6. Softening or degeneration of the tumor.
7. Inflammatory lesions within the pelvis, especially inflammation of the adnexa.
8. When the tumor and uterus is larger than a four months pregnancy.
9. Submucous tumors, especially if pedunculated.
10. Young patients.
11. Marked anemia out of proportion to the symptoms and clinical findings.
12. Obstructing tumors or malformations which prevent the proper application of the radium.
13. Radiophobia.

DOUBTFUL DIAGNOSIS.—To consider these contraindications less briefly, it will be observed that we have placed a doubtful diagnosis in the first place. We have previously stressed the necessity for an accurate and complete diagnosis prior to irradiation. Important as this is in any case, it is doubly so in the case which is to be treated by irradiation. Mistakes in this point are likely to result in disastrous consequences. It is far safer for the competent surgeon to operate upon than to irradiate a case in which the diagnosis is uncertain. On account of the relaxation which it produces, ether is preferable to gas anesthesia in doubtful cases. Because of

the necessity for certainty in diagnosis it is unwise for irradiation to be performed by any but those competent in gynecologic examinations. It is for this reason it is unsafe for the average radiologist and X-ray expert to perform this operation. On one occasion one of the authors made a small abdominal incision for diagnostic purposes. The patient weighed 270 pounds and despite the thickness of the abdomen walls this seemed the safest course. A small uncomplicated myoma was found, the incision closed and radium applied. Whereas this was an exceptional case, we quote it in order to emphasize the importance of accuracy in diagnosis.

OTHER INTRAPERITONEAL LESIONS.—The presence of intraperitoneal lesions other than the myoma which require surgical intervention is by no means an absolute contraindication to irradiation and indeed may be an indication for its use.

If the appropriate treatment for a diseased gall-bladder, stomach or appendix is difficult, time-consuming, or the patient's general condition not satisfactory, considerable time may be saved by irradiation after the completion of the intraperitoneal work with the advantage of the certainty of diagnosis which inspection and intraperitoneal palpation have permitted. As a general rule, however, if it is necessary to open the abdomen operation is preferable to irradiation.

RAPID GROWTH.—Rapid growth is suggestive of malignancy. Myoma may undergo sarcomatous degeneration or a sarcoma may closely simulate a myoma. The treatment of choice for sarcoma has been previously referred to and is operation and not irradiation alone certainly in the type of sarcoma which is likely to be mistaken for a myoma.

ASSOCIATED NEOPLASMS, SUCH AS FUNDAL CARCINOMA OR OVARIAN TUMORS.—Such tumors are best treated by hysterectomy and bilateral salpingo-oöphorectomy, regard-

less of the myoma which is of secondary importance and is removed incidentally.

PRESSURE SYMPTOMS.—Pressure symptoms are more prone to develop in larger tumors which in themselves are less favorable to irradiation than are the smaller neoplasms. But of greater importance is the fact that the shrinkage of the tumor following irradiation often requires months and in some cases does not occur at all. Operation is, therefore, safer and quicker.

Gauss and Friedrich⁸ secured shrinkage or disappearance of the tumor in 70–80 per cent. of cases. Polak⁹ observed shrinkage to one-half the original size in 80 cases and disappearance in 20 in a series of 106 cases, or shrinkage, or disappearance in about 75 per cent. In a series of large myomata irradiation, Burnam¹⁰ secured shrinkage in 50 per cent. of cases. In the Gynecologic Department of the University Hospital, considerable shrinkage or disappearance of the tumor has occurred in about 65 per cent. of cases in from six months to one year. Tumors which are chiefly intramural are most likely to undergo shrinkage, and the pedunculated subperitoneal variety are least affected.

DEGENERATION OF THE TUMOR.—Softening or degeneration of the tumor is of frequent occurrence in myomata. Doubtless many tumors, the seat of less pronounced grades of degeneration, are not recognized and subjected to irradiation with uniform success, but when the degeneration has reached a stage when it is readily determinable by clinical methods, operation is indicated. By its local action and by reducing the blood supply, irradiation is likely to augment the degeneration. Furthermore it is probable that advanced degenerative changes in a myoma produce by absorption more or less toxemia, and even if irradiation eventually

reduces the tumor to a hard shrunken innocuous neoplastic mass, the process would be too slow. Radium has no effect upon calcareous tumors.

INFLAMMATORY, INTRAPELVIC LESIONS, ASSOCIATED WITH MYOMATA.—The most frequent of these is inflammation of the adnexa. Polak¹¹ found this present in 54 per cent. of his cases. Kelly and Cullen¹² found inflammatory adnexal lesions in 35.6 per cent. of white and 63 per cent. of colored myoma patients; McDonald,¹³ in 27.5 per cent. of 700 cases; Frank¹⁴ in 18 per cent. The proportion of adnexal lesions varies considerably according to the character of cases utilized for study. It is considerably higher among the colored race and in some of the Southern clinics inflammatory lesions are encountered in nearly 90 per cent. of cases.

Irradiation in the presence of inflammatory adnexal lesions is likely to produce an active peritonitis and is a definite contraindication to the intrauterine use of radium. That irradiation does not always light up the infection is certain.

One of the writers recently performed a diagnostic curettage followed by an intrauterine application of 3500 mg.h. upon an extremely stout patient. An adenocarcinoma was present and six days later an abdominal hysterectomy was performed. The pelvis was a mass of old adhesions, a pyosalpinx and ovarian abscess were present on one side and a tubo-ovarian abscess upon the other. Despite these lesions, convalescence from the D. and C. and irradiation was uneventful, the temperature never going above 99° F. and no clinical manifestation of peritonitis occurred. The most careful questioning failed to elicit any past evidence of the trouble. Furthermore, convalescence from the hysterectomy was unusually satisfactory. Many other more or less similar cases could be cited. Despite our precautions it seems prob-

able that occasionally in any large series of cases submitted to irradiation, an adnexal lesion will be unrecognized. Despite this even mild evidences of infection are extremely rare following irradiation. In considering the question of an exacerbation of an old pelvic inflammatory disease following irradiation, it must also be remembered that a simple dilatation will often light up a peritonitis. Van de Velde¹⁵ and others have actually recommended irradiation for the treatment of pyosalpinges. We mention this merely to demonstrate that irradiation does not always produce trouble. Such treatment is, in our opinion unjustifiable and inflammatory lesions an absolute contraindication of irradiation.

Encapsulation tends to destroy many of the microorganisms which produce pelvic inflammatory disease and it is likely that only when active organisms are present will radium produce an exacerbation. However, there is no clinical method of determining this point with certainty and the only safe procedure is to refrain from irradiating all cases in whom adnexal lesions are present. Furthermore, many of these patients suffer quite as much, if not more, from the adnexal lesions than from the tumor, and even if irradiation relieved the symptoms arising from the latter, the result would still be unsatisfactory. In the Gynecologic Department of the University Hospital, irradiation has been refused to all cases in which palpable findings were even suggestive of an inflammatory lesion.

A history suggestive of inflammatory lesion is also a contraindication. A history indicative of gonorrhea or a slight rise in temperature following the pelvic examination or leucocytosis is always suggestive of an adnexal complication.

LARGE TUMORS.—When the myomatous uterus is larger than a four months pregnancy, irradiation is generally con-

traindicated. Both authors have repeatedly irradiated tumors much larger than this with entire success. Burnam¹⁶ recently reported satisfactory results in a series of 30 cases of large myomata. Irradiation is not, however, the method of choice except in exceptional cases, such as those in whom operation is unusually hazardous, due to cardiac decomposition or some other surgical contraindication.

Refusal to permit an abdominal section, hemophilia, pulmonary tuberculosis, etc., or other complications may be present, which make operation extremely hazardous, and yet on account of the severity of the pelvic symptoms relief must be obtained, under such circumstances, irradiation is the method of choice. Hemorrhage can be checked with nearly as great certainty in large as in small tumors, but the relief from pressure symptoms is uncertain and slow. Furthermore complications of all kinds are more frequent with large than with small tumors.

A larger dosage of radium is required when treating massive tumors and many operators combine X-ray with the treatment. If, for some reason, operation is inadvisable, the combination of X-ray and radium would seem a logical one. Believing as we do that action of the radium upon the ovary is the chief factor in producing the beneficial results, it would appear probable that in the presence of a large tumor, one, or even both ovaries might well be beyond the range of effective intrauterine irradiation, especially if the endometrial cavity were much distorted as is often the case.

SUBMUCOUS TUMORS.—Submucous myomata, especially when pedunculated, are usually best treated by operation. This is a contraindication which requires qualification. Pedunculated submucous tumors are best treated by operation; such myomata can often be removed by a simple vaginal

myomectomy. This variety is more likely to be single than any other type. Submucous tumors, on account of the expulsive action of the uterus and their close association with the vagina, are often degenerated and the seat of an infection. Irradiation is slow, is likely to, temporarily at least, increase the degenerative process and light up the infection. On the other hand, intramural tumors which are partly bulging into the endometrial cavity, respond readily to irradiation. As in all contraindications, cases must be judged individually.

YOUNG PATIENTS.—Myomata in young women are usually best treated by operation. Twenty-four hundred milligram hours of irradiation usually produces a permanent amenorrhea simulating in its clinical effects a bilateral oöphorectomy. Smaller doses are less certain in their effects. It follows, therefore, that a dose sufficient to ensure a clinical cure is followed by the symptoms of an artificial menopause, which apart from the sterility incurred are often as disagreeable as the effects of the tumor. The most satisfactory treatment for this class of case is myomectomy, and if this is not feasible a high supra-vaginal hysteromyomectomy with conservation of the tubes and ovaries. If myomectomy is possible all the functions of the genital tract may be preserved and if it is necessary to sacrifice the top of the uterus, only fertility is lost. The ultimate results fully justify the slightly greater risk incurred by operation. In special cases irradiation may be indicated but the dosage should be reduced to 400–600 mg.h. and may have to be repeated and may even then fail.

There is no doubt that cases respond differently and the safest course in young patients is to employ the minimum dosage. If this is done the results are less certain and recurrence more likely. Ovaries of young women are probably less susceptible to the action of radium than are those of women

of more advanced years. An advantage of irradiation is that its employment in no way mitigates against a subsequent operation, and furthermore the use of radium is almost without mortality.

TUMORS ASSOCIATED WITH MARKED ANEMIA AND A CACHECTIC APPEARANCE OF THE PATIENT.—Uncomplicated marked anemia is an indication rather than a contraindication to irradiation, as anemic patients are less favorable surgical risks and are especially susceptible to infection and other postoperative complications. The point we wish to emphasize is that brought out by Keene.¹⁷ Myomata, associated with a cachectic appearance of the patient and with an anemia out of proportion to the quantity of blood lost, are not as a rule favorable subjects for irradiation. We have observed several such instances which were explained by the absorption of toxic material from a necrotic or degenerated tumor.

OBSTRUCTING TUMORS OR MALFORMATIONS.—Obstructing tumors or malformations which prevent the proper application of the radium are obviously a bar to its successful employment. Such cases are extremely rare. Cervical myomata do not respond well to irradiation and for this reason the presence of tumors of this type when found in combination with corporeal myomata are generally a contraindication to irradiation.

RADIOPHOBIA.—We have added radiophobia to our list of contraindications because Keene has encountered one such case. It is needless to state that these cases are extremely rare. The fact that the lay mind is so imbued with the idea that the employment of radium therapy implies the presence of a cancer accounted for the one case that has come to our knowledge. Graves¹⁸ mentions retention cysts of the follicu-

lar type as a contraindication to irradiation and states that these may subsequently become enlarged and troublesome. We have not encountered this complication and are inclined to believe that small retention cysts have probably been present in many of our cases. Graves also refers to the mistake of irradiating patients in whom perforating (Sampson's) cysts are present.

Sampson and the writers have found these cysts present in a large proportion of myomata. One of the most frequent results of the Sampson cyst is the development of adhesions. Adhesions are frequently painful. Irradiation will not cure adhesions and to this extent irradiation is contraindicated. Other than this irradiation is not likely to cause trouble; indeed the artificial menopause induced by the irradiation would almost certainly check the further development of these lesions. The proliferation of the endometrium within the Sampson's cyst is dependent upon the ovarian stimulus as is the uterine endometrium.

It is well known that these cysts cease to develop after the menopause. There is no way of differentiating with certainty a small Sampson's cyst from a large but otherwise normal ovary or from a normal corpus luteum prior to opening the abdomen. It is likely that many cases of small Sampson's cyst have been treated successfully by irradiation without being recognized. When well developed, Sampson's cysts produce quite characteristic symptoms, pain being a pronounced feature. The palpable findings are also well marked and often resemble inflammatory tubo-ovarian disease. We have already warned against employing irradiation in cases presenting these symptoms.

From the foregoing it is evident that either myomectomy or hysteromyomectomy is the preferable treatment in the

majority of cases. In many cases, however, irradiation is the method of choice and any other treatment submits the patient to unnecessary risks and certainly does not produce better if as good results. Irradiation is the method of choice in (a) small or medium-sized uncomplicated myomata whose chief symptom is hemorrhage, (b) in myopathic hemorrhage, but in younger individuals should be employed cautiously for fear of the production of a permanent amenorrhea and sterility and other symptoms of the artificial menopause, (c) and in all cases in which surgery is contraindicated, such as the presence of cardiac, renal or pulmonary disease or other conditions which would make operation unduly hazardous. Graves,¹⁹ Taussig²⁰ and others have directed attention to the complications which may follow irradiation; the chief one of these is that there may be a recurrence or continuance of the bleeding. Patients respond differently to irradiation as incised by the fact that some tumors apparently disappear whereas others submitted to the same dosage and apparently similar in all respects, do not, or shrink only to a much less extent.

After irradiation the uterus and ovaries are still present and a recurrence of bleeding is therefore possible. The same is true in the case of a myomectomy. A little less than 5 per cent. of our cases have suffered a recurrence of bleeding sufficient to require a second treatment. The majority of these have been younger women in whom the irradiation dosage has been small. One irradiation by no means contraindicates a second treatment, and a recurrence can be usually cured in this way. Furthermore, intrauterine irradiation in no way mitigates against the success of a subsequent operation although this in our experience has been rarely necessary.

The irradiation of a sarcoma in the belief that the tumor

was a myoma, was formerly stressed as a serious danger incident to this form of treatment. We believe that it has been greatly overestimated. In none of the 550 cases of benign uterine hemorrhage which have been treated in the Gynecological Department of the Hospital of the University of Pennsylvania has this occurred. Sarcoma is a relatively rare tumor and sarcomatous degeneration of myomata is also infrequent. In the Gynecological Laboratory of the University of Pennsylvania it has been found that sarcoma and sarcomatous degeneration constitute less than 0.5 per cent. of all connective tissue new-growths of the uterus. It is now well recognized that the former high estimates regarding the frequency of sarcoma, as high as 10 per cent. from some clinics, was due to an erroneous histological diagnosis. Extremely cellular areas or areas of benign degeneration are of frequent occurrence in fibromyomata and may occasionally cause confusion to the inexperienced pathologist. The possibility that a sarcoma may be mistaken for a myoma and treated by irradiation should, however, be borne in mind. If each case is carefully studied prior to the institution of treatment, the likelihood of such an erroneous diagnosis being made is extremely slight.

Dangers of mistaken diagnosis must be constantly in mind and for this reason we strongly deprecate irradiation of gynecologic cases, by any but experienced pelvic surgeons.

Nausea during the period of irradiation is not infrequent; we believe it is somewhat more frequent than following a simple dilatation and curettage. It is certainly not so frequent, severe or prolonged as generally occurs following a hysterectomy or other intraperitoneal operation. If present it disappears almost uniformly and immediately with the removal of the radium from the uterus. In many cases it is

entirely absent and only in rare instances is it severe. Anesthesia, narcotization and the presence of a foreign body within the uterus doubtless account for the majority, if not all the cases. The remarkable uniformity with which the nausea immediately ceases upon the removal of the radium from the uterine cavity is suggestive of the foreign body explanation. If the nausea were a specific result of the action of the radium it would appear likely that it would continue for some hours at least, after the withdrawal of the latter.

Irradiation is generally employed in the worst cases, many of which are unfavorable risks from an ordinary surgical viewpoint and would be expected to develop various postoperative complications. We have not observed persistent or severe nausea which could not be explained on grounds other than irradiation. This complication appears to have been overstressed by some writers. The usual treatment employed for postoperative nausea should be given in the cases in which this complication is present. Graves²² observed a case in which persistent nausea and vomiting continued for a week. Such instances must be rare and other causes than the irradiation should be sought. We have not encountered such an instance among our rather large series.

In a small proportion of cases leukorrhea may be a postoperative complication of irradiation or more frequently a continuance of previously present leukorrhea may be observed. The most common preoperative leukorrhea occurs at the cessation of the bleeding as a thin pink or pale discharge generally lasting for a few days or a week. This type of leukorrhea may continue for some weeks following the postirradiation amenorrhea. Leukorrhea due to a lacerated cervix is likely to continue for a like or even longer period. The cessation of this later type of leukorrhea is analogous to

the cessation of leukorrhea which occurs from similar causes at the normal menopause except that in the former case the continuance of the discharge is of shorter duration. Leukorrhea may develop as a postirradiation symptom due to improper screening or application of the radium. With the present standardization of technique this should not occur. Postirradiation leukorrhea of a sufficient amount to be a pronounced symptom is rare and can be satisfactorily treated by cleanliness and the administration of a douche. Preëxisting leukorrheas are frequently cured by irradiation.

PAIN.—A certain amount of colicky pain is often present during the period of irradiation doubtless due to the presence of a foreign body within the uterus. After the withdrawal of the radium pain is of rare occurrence and if severe is an ominous symptom, suggestive of the presence of an inflammatory adnexal lesion which had been overlooked.

The production of irradiation menopause has already been considered. This occurs with about the same frequency and intensity as follows a bilateral oöphorectomy. In a previous study²³ we compared the end-results secured in a series of uterine myomata and pelvic inflammatory cases in an effort to determine the chief factors accountable for the production of severe climacteric symptoms. The conclusions arrived at in that investigation have been confirmed in the study of the irradiated cases.

As a general rule, the younger the patient the more pronounced are the menopausal symptoms. This is true in the studies of series of cases but is by no means always the case with an individual patient. An even more important factor is the temperament and nervous stability of the patient. Some of the women who suffered most severely from artificial menopause in both the groups submitted to complete

operation and the irradiated cases occurred in women of over 40 years of age. Highly neurotic or over-sexed individuals are likely to suffer more than are those of a phlegmatic type. For this reason patients should be studied individually and this fact borne in mind in the border-line cases in which it is questionable whether irradiation or operation shall be the method of treatment. This is particularly true of those patients in whom it appears likely that a hysterectomy and conservation of the ovaries would cure the condition.

Serial studies have shown that when a dosage of 1200 mg.h. is employed, climacteric symptoms other than the mere checking of the menstrual function in varying degrees of intensity will be produced in 60 per cent. of patients. In 36 per cent. the symptoms will be marked. As a rule they persist for from a few months to two or three years and then subside. With the smaller dosage of from 300 to 400 mg.h. recommended for young women, in no case in our series has permanent amenorrhea been induced. Our observations substantiate the experimental work of Matthews²⁴ and others who have found that the ovaries of young animals are more resistant to and exhibit greater regenerative powers after irradiation than do similar organs in older subjects.

The vast majority of women requiring irradiation are past the child-bearing age or the possibilities of conception and subsequent normal pregnancy has ceased because of distortion in the uterus incident to the presence of a myoma. As we have previously indicated, our inclination is toward operation rather than irradiation in younger patients. Five patients in our series of 527 cases, or somewhat less than 1 per cent., have subsequently become pregnant. The vast majority of women in the series were past the child-bearing period. In many the myoma itself made conception unlikely and

successful pregnancy extremely improbable, and others were spinsters.

Case I: A woman aged 29 suffering from persistent menorrhagia, in whom three previous curettements had failed, was treated with 225 mg.h. Menses became normal and two years later she was delivered of a healthy, full term infant. There was no recurrence of the menorrhagia.

Case II: A young woman aged 31 who had suffered from an excessive menorrhagia for ten years, produced by a myoma the size of an orange. Her general condition contra-indicated operation. Subsequent to an irradiation of 1200 mg.h. she passed through a definite menopause cycle. The periods returned later and pregnancy occurred. The pregnancy progressed normally to term. She succumbed to a postpartum hemorrhage following a difficult forceps delivery.

Case III: Pregnancy occurred two years after 1200 mg.h. irradiation but resulted in a miscarriage.

Case IV: In this case a normal delivery occurred three years after a 200 mg.h. irradiation. The menorrhagia was cured.

Case V: The patient had twice received applications of 300 mg.h. each. She subsequently became pregnant three times. All of these pregnancies resulted in premature and dead infants. This patient was syphilitic and neglected treatment.

In none of the cases was there any evidence of malformation of the infant, such as Guyer, Smith,²⁵ Bailey, Bagg,²⁶ Little²⁷ and others have suggested irradiation may produce by injury to the ovum.

Numerous instances of successful pregnancies following irradiation have been recorded by Polak,²⁸ Schmitz,²⁹ Stacy³⁰ and many others.

When pregnancy is desired the question of choice between operation and irradiation must be carefully considered. If it seems likely that a myomectomy is feasible, this is generally the preferable procedure although small doses of radium may be tried. These cases should be studied individually. When it appears that a single myoma is present upon which a myomectomy can be satisfactorily performed, this is certainly the treatment indicated. When, however, it is questionable whether myomectomy is applicable on account of the number or situation of the tumors a trial of small doses of radium is preferable.

It should be borne in mind that if pregnancy follows myomectomy the dangers of rupture of the uterus due to weakening of the myometrium as a result of the cicatrix is to be considered and Cæsarian section may be advisable. Little can be accomplished for cases of myopathic hemorrhage by operation as far as subsequent pregnancy is concerned and it is in these cases that small doses of radium, if necessary repeated, offer a decidedly better chance of subsequent childbirth than does operation. From experimental evidence it would appear that if conception occurs shortly after an irradiation the resulting fetus might be injured due to the action of the rays. From a practical standpoint this is unlikely.

METHOD OF TREATMENT.—Having decided that irradiation is indicated in any given case the usual preoperative safeguards should be employed. In anemic patients a blood transfusion either before or at the time of irradiation is advisable. 500 cc. is sufficient in the majority of cases. In markedly anemic patients who have been untreated prior to their arrival at the hospital, a period of rest in bed, ice bag over the lower abdomen, light nourishing, easily digested

diet, calcium chloride, ergot and the usual methods to check hemorrhage may be tried in an effort to improve the general condition prior to the irradiation. If the hemorrhage is still definitely periodic in type, irradiation may be well delayed until a few days prior to the expected bleeding, in this manner giving the patient the benefit of the recuperation incident to the absence of flow. Transfusion is of the greatest value. It lessens the likelihood of the development of complications and shortens convalescence. Ordinarily nitrous oxide and oxygen anesthesia is employed. If there is any question regarding the correctness of the diagnosis and greater relaxation is required in order to permit a more satisfactory pelvic examination, nitrous oxide followed by ether is the method of choice. It is far preferable to submit a patient to the greater discomforts of ether anesthesia than to irradiate in the presence of a contraindication. Ether is only necessary in exceptional cases. In a few cases we have applied radium under local anesthesia when the patient's general condition has not warranted even a light nitrous oxide anesthesia. The curettage in these cases is necessarily incomplete and the procedure is not to be recommended except in exceptional cases.

TECHNIQUE.—Under anesthesia a careful pelvic examination is performed. The size of the uterus is estimated and the depth of the endometrial cavity measured with a sound and recorded for future reference. A thorough curettage is performed and the curettings preserved for a histologic examination. The radium or emanation properly screened and encased in a rubber tube is inserted to the fundus of the uterus. This rubber tubing is about one centimetre longer than the uterine cavity. This ensures easy withdrawal. Around the lower end of the tube is tied a no. 1 catgut suture;



FIG. 48. —Showing radium and capsule and method of encasing in rubber tube.

one end of this is stitched through the cervix and clamped with a hemostat and the end cut short. This ensures the maintenance of the radium in the desired position. When the radium is to be removed the hemostat is taken off and the tube is then easily withdrawn. Twelve hundred milligram hours is our standard dose and is usually secured by applying 50 mg. of the element for 24 hours.

If a greater quantity of radium or emanation is available the same effect may be produced by applying a more intensive irradiation for a shorter period with the advantage that the discomfort of the intra-uterine application is shortened. Except for the withdrawal of the radium, the after-treatment is similar to that given to simple curettage cases. As a rule these patients remain in the hospital for five days. No douches are administered. It is unwise to permit the patient to go home earlier since the surgeon should see the patient through any possible complication arising from his surgical intervention. Our rule is that all irradiation patients return for examination six to eight weeks after treatment. If the patient cannot

return because of living at a distance or for other reasons, a personal letter from her or from her attending physician is

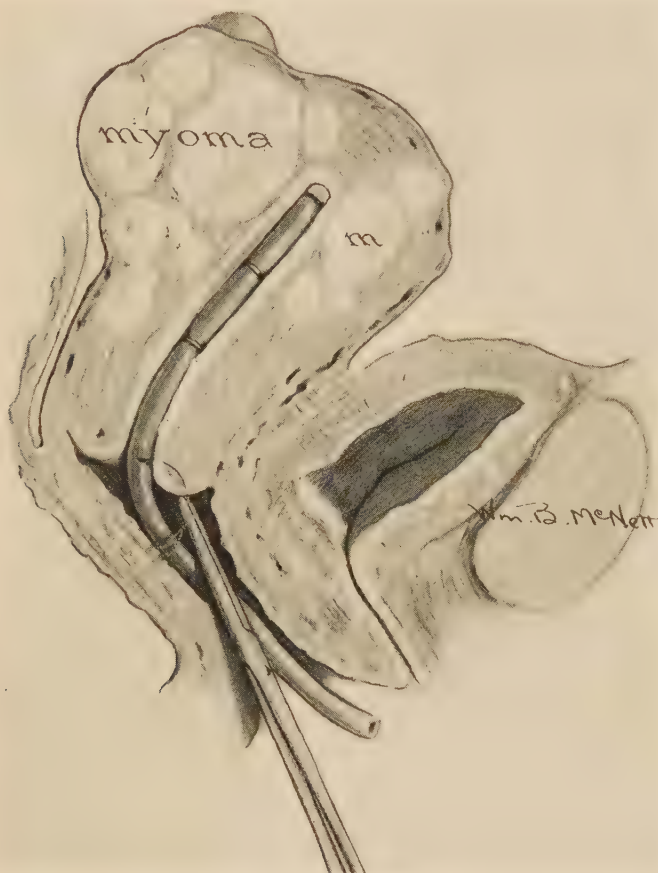


FIG. 49.—IRRADIATION FOR UTERINE MYOMATA.—Two 25-mg. capsules of properly screened radium encased in a rubber tube are introduced into the uterine cavity. A preliminary curettage has been performed and the curettings procured for histologic examination. The radium is maintained in position by the stitch as shown. A light gauze pack is introduced into the vagina. When irradiating patients over 40 years of age for hemorrhage of benign origin, 1200 mg.h. of radium is employed.

requested. The usual rigid follow-up, covering a minimum period of one year (in benign cases) is carried out. No special after-treatment is required in the average case other than

good hygiene, regulation of the bowels and an opportunity to recover from the effects of the anemia which has often been present.

RESULTS.—Clark and Keene³¹ have recently analyzed the results of 527 cases of benign hemorrhage from the uterus due to myomata or myopathic hemorrhage. Four hundred and seventy-six cases were available for end-result study; of the remaining 51 some have not been heard from and others were too recently treated for conclusive study. Not infrequently, after irradiation, one, occasionally, two, rarely three menstrual periods occur prior to the onset of the permanent amenorrhea. Individual patients vary in this respect.

The period of the menstrual cycle in which the irradiation is performed has a bearing upon this point. If the irradiation is performed shortly before the expected period it is less likely to influence the expected flow. Usually within four to six weeks at most, structural changes induced by the irradiation will have progressed sufficiently to check all bleeding. On this basis Gellhorn³² recommends irradiation soon after a menstrual period and this is undoubtedly the time of election. On the other hand, delay in this respect may result in the extremely anemic patients losing what advantage they have gained by the often short period of absence of flow. Again we would here emphasize that patients must be judged individually to ensure the best results. All patients should be warned that the action of the radium is often slow and they should not be discouraged if amenorrhea is not produced at once. Among the 476 cases in which an end-result study was possible, 91 per cent. were cured either by the production of a permanent amenorrhea, or a temporary amenorrhea was produced followed by a re-

turn to the normal of the amount and periodicity of the menses.

Among the 527 cases one death occurred; this patient was very stout and within 24 hours after a plastic operation upon the vagina accompanied by a simple dilatation, curettage and the intrauterine application of 50 mg. of radium she developed severe pain in the epigastrium which soon defined itself as a general peritonitis from which she died. A necropsy was not permitted. It is possible that there was an unrecognized lesion in the upper abdomen and the ultimate catastrophe resulted from the perforation of an ulcer or possibly from some accident incident to an hepatic or pancreatic lesion. The mortality from the series was therefore 0.18 per cent. Among the 476 cases recurrence of bleeding occurred in 47 cases. In 23 of these 47 cases the bleeding was merely a return to the normal menstruation. Six cases were cured by a second irradiation and 18 cases were ultimately submitted to operation. In the majority of the cases which finally came to operation the general condition of the patient was far better, due to a period of irradiation amenorrhea than if operation had been forced upon the surgeon at the time the patient was first observed.

In the entire series of 476 cases, therefore, the pathologic bleeding was cured by irradiation in 96 per cent. and operation was subsequently required in 3.7 per cent. of cases. The irradiation mortality was a little below 0.18 per cent.

Taussig³³ collected statistics formulated from nearly 1100 cases of myoma treated by irradiation, showing 95.5 per cent. of cures. Numerous statistics could be quoted. We believe the above results demonstrated the average incident of cure in properly treated cases and that further citation is therefore unnecessary.

Among the 527 cases postoperative complications occurred as follows: phlebitis developed in two cases; in one a recurrence of an old lesion. In the second a bilateral phlebitis followed a combined irradiation and extensive plastic operation. Eight patients developed neuritis, which is not an infrequent occurrence in women at the menopause regardless of antecedent treatment. There is little need for comparison between surgery and irradiation in the treatment of uterine myomata. The indications for surgery are well defined. Myomectomy and hysteromyomectomy are among the most satisfactory operations which the surgeon is called upon to perform both from the immediate and end-result standpoint. However, the advantages of irradiation in certain types of cases are well proven and the surgeon who submits these patients to operation is incurring an unwarranted risk and will in the long run secure less successful results. Surgery is associated with an operative mortality of from 2 to 7 per cent., even in the most experienced and skilful hands, a clear salvage of from 1.82 to 6.82 per cent. Markedly anemic patients are notoriously poor surgical risks and are the very type in which radium secures its most brilliant results. The figures we have given are conservative and were the patient familiar with the facts, few who are suitable for irradiation would submit to operation. Radium is now available in most well-equipped hospitals and lack of this element or unfamiliarity with its use cannot, with justice, be advanced as an excuse for an unnecessary and more hazardous operation that is followed with inferior results.

Excellent results have been secured in the treatment of uterine myomata by the X-ray. The disadvantage of the X-ray apart from the fact that the treatment is prolonged, lies in the fact that a curettage must be performed to exclude

the possibility of overlooking the presence of a fundal carcinoma. If we accept the necessity for a routine diagnostic curettage, it is far easier, for the patient, to irradiate at the same sitting rather than prolong the procedure over weeks or months, with no better, if as good, end-results. The incident of fundal carcinoma and myomata is relatively frequent. It is unlikely that the experienced surgeon will not at least suspect the presence of a fundal carcinoma in an individual case. In large groups, however, occasionally such a mistake will be made due to the preëxisting symptoms from the myoma completely masking those of the carcinoma.

We have previously mentioned that 75 per cent. of failures to recognize the presence of fundal carcinoma in our series of 101 cases reported by Norris and Vogt³⁴ from the Gynecologic Department of the University Hospital, was due to this fact. We, therefore, believe that a curettage followed by a histologic examination of the curettings by a competent gynecologic pathologist is an essential feature of every irradiation for hemorrhage of a supposedly benign origin. Neglect of this detail is to court trouble. The amount of irradiation generally applied for benign hemorrhage lacks about 4000 mg.h. from that required for the most successful treatment of fundal cancer apart from the fact that hysterectomy is more effectual than even the maximum irradiation. A combination of radium and X-ray irradiation may be well utilized in the treatment of large tumors in which removal is contraindicated. The contraindications to X-ray therapy are the same as for irradiation by radium.

HEMORRHAGES OF BENIGN ORIGIN OTHER THAN THOSE CAUSED BY MYOMATA.—Many pelvic and a few general conditions may result in pathologic uterine hemorrhage. It is unnecessary to enumerate these various conditions. In the

so-called myopathic hemorrhage irradiation is practically specific. Whether we accept an ovarian, myometrial or endometrial theory regarding its etiology is of no special importance as far as treatment is concerned as experience has amply demonstrated that irradiation is an almost certain cure in all cases. These hemorrhages are most prone to occur in women over 40 years of age and are therefore especially suitable for irradiation. Occasionally myopathic hemorrhages occur in younger women and the problem of operation *vs.* irradiation becomes an important one. If a high supravaginal hysterectomy with conservation of the ovaries, or a Blair-Bell operation is performed, the patient is sterilized, and faces a small operative mortality.

On the other hand small doses of radium are uncertain in their effect. We prefer in these cases to perform a curettage and apply from 200 to 300 mg.h. of radium. This dosage is almost certain not to produce a permanent amenorrhea; if the hemorrhages are not checked a reapplication of the radium may be made without curettage. We have treated one or two cases four times, each treatment producing amenorrhea for one to four months, then normal flow followed for a few months and finally a recurrence of the excessive bleeding. Other cases have been ultimately cured. If the irradiation is entirely ineffectual or recurrence continues, operation must be resorted to. These cases must be individualized. If future child-bearing is of little moment to the patient, operation is often the most satisfactory procedure for by it the bleeding can be checked with certainty and if the ovaries are conserved the development of the artificial menopause is not incurred. To other patients possible pregnancy may mean everything and in these minimum doses of radium should be tried.

As we have previously emphasized irradiation is by no means the ideal treatment for young women but in some cases may be preferable to operation and at least warrants a trial. In all young women minimum doses should be employed despite the knowledge that in a definite proportion of cases failure will result. This is far preferable to the production of a permanent irradiation amenorrhea with its accompanying menopausal symptoms and sterility.

DIFFUSE ADENOMYOMA OF THE UTERUS.—It is the general experience that these cases do not do well under irradiation and this has been the case with the few such tumors of this variety that have come under our observation. It seems proven that some of these tumors owe their origin to a trans-tubal migration of particles of endometrium as pointed out by Sampson, in others this is less certain. Certainly many of these neoplasms are associated with adnexal adhesions and even although active infection may not be present, this should constitute a contraindication to irradiation. The rather characteristic symptoms produced by diffuse adenomyomata should render diagnosis easy.

Adenomyoma in general constitutes about 7 per cent. of all uterine myomata. In the diffuse variety the amount of endometrium present is relatively considerable, whereas in the circumscribed type this tissue is generally present in a much lesser amount. There is no way in which a circumscribed adenomyoma can be differentiated from a fibromyoma with any degree of certainty prior to operation, and as a few endometrial-like glands are present in about 2 or 3 per cent. of all cases of myomata, it appears certain that in any large series many of these are submitted to irradiation unwittingly and with entire success.

Hemorrhages due to constitutional causes are usually

best treated by treating the cause; occasionally, especially in middle-aged patients, irradiation may be advisable in order to check the bleeding which may in itself be a definite handicap to recovery.

MYOMA UTERI TREATED BY IRRADIATION.—The patient is a white woman 46 years of age. She is a widow, her husband having died three years ago. She was married at 30 years of age and was never pregnant. Menses began at 14, occurred every 28 days with a duration of four or five days. There was slight pain or discomfort for the first two days but with this exception there was never any dysmenorrhea. The flow was normal in amount, the patient generally using two or three pads per day. She has never had any leukorrhea. Her general health has been good until the present illness.

About two years ago she noticed an alteration in the menstrual flow. This was at first manifest by an increase in the duration: instead of lasting four or five days as formerly, the flow continued for five or six days, then seven or eight days; the duration gradually increased until for the last five or six months the flow has been almost continuous, sometimes lasting for three to five weeks and all track of the normal periodicity has been lost. With the increase in the duration of the menstrual period began an increase in the amount of flow. At first this was slight but later double the number of pads were required daily. At present she bleeds most of the time with intervals of cessation which vary from a few days to a week or two. Sometimes, the flow is very profuse but more often it is in the nature of a gradual leakage. The number of pads required varies from two to twelve for 24 hours. The flow is painless.

Upon the cessation of the flow there is a rather thin, sometimes blood-stained leukorrhea which continues for a

day or two. It is noticeable that the bleeding is more profuse when the patient is upon her feet and before she became incapacitated was augmented by hard work. As a consequence of the prolonged hemorrhage various symptoms incident to anemia have developed. She feels weak, giddy, suffers from headaches, and for the past two months has been confined to bed. Even getting up to go to the toilet causes an increase in the flow. She is unable to walk without help and staggers and would fall if left to herself when upon her feet. She has no pelvic pain. The bowels have been regulated by cathartics since confinement to bed. She has lost 17 pounds in the last six months.

Physical examination shows a large ill-nourished woman who looks older than her stated age. She is thin and her face careworn. The most striking feature is her marked pallor, the skin of the face and hands being like wax. The lungs are normal, the heart sounds are weak, no murmurs are present. The temperature is 98, pulse 88 soft and occasionally intermittent, the respirations are 18 but rapidly rise on exertion as does the pulse. The systolic pressure is 90 and the diastolic 60.

Urine analysis is negative and the quantity is normal. Blood analysis shows the hemoglobin 19; R.B.C. 3,400,000, W.B.C. 4000, coagulation time four minutes.

Abdominal examination is negative. Pelvic examination shows normal external genitalia, vagina and cervix. The place of the fundus is taken by an irregular, hard, nodular, movable, non-tender mass which is evidently a myomatous uterus. This is about the size of a two and one-half or three months' pregnancy. There is no tenderness laterally, both ovaries can be palpated and the adnexa on both sides is evidently normal.

Diagnosis: fibromyoma of the uterus, normal adnexa, and marked anemia incident to the prolonged and profuse menorrhagia.

Advise diagnostic curettage and irradiation preceded by a transfusion.

It was impossible to procure a suitable donor and operation was performed without delay. The patient was prepared for operation in the usual manner. One hour before anesthesia, one-quarter grain of morphine sulphate was administered by hyperdermic. Operation, nitrous oxide gas, anesthesia, curettage followed by the insertion of 50 mg.h. of radium. Note at operation—the cervix was easily dilated and a blood clot was found in the uterine cavity. It was noticeable that the blood was very watery and pale. Upon curettage a small tumor could be felt slightly projecting from the posterior uterine wall. This tumor was estimated as the size of a walnut and perhaps one-fifth of its bulk was submucous. The endometrium was normal in amount and to the naked eye. The uterine cavity was 5.5 cm. in depth. Two capsules each containing 25 mg. of radium were placed tandem fashion in the fundus and stitched in place in the usual manner. A slight vaginal pack of gauze was introduced.

CONVALESCENCE.—The radium was left in place 24 hours (1200 mg.h. dose). Catheterization was not necessary, the patient being able to void normally. On the third day the bowels were moved by a small low soap suds enema and the patient gotten in a wheeled chair and thereafter was kept as much as possible in the sun and out of doors (May). Nourishment was pushed. At the end of a week the general condition of the patient was improved, hemoglobin 30, systolic blood pressure 100 and the patient was allowed to return to her home. One month after operation the hemo-

globin was 55, blood pressure 110. Patient still feels a little weak but otherwise believes herself cured. Three months after operation the hemoglobin is 85 per cent., blood pressure 128. Patient looks and feels well, no symptoms are present. Pelvic examination shows tumor of same size as at operation. The general health continued excellent, at the beginning of the sixth month the uterine tumor was perhaps slightly shrunken, by the ninth month this shrinkage was well marked and at the completion of the year from the time of operation the uterus was normal in size and depth. There has been complete amenorrhea. During the third month the symptoms of the artificial menopause appeared, but were not very severe. After the ninth month these symptoms gradually diminished. From the sixth week to the third month there was a moderate amount of rather thin non-odorous leukorrhea present. This was never enough to require the wearing of a pad. For a short time this was taken care of by a daily vaginal douche, then the douche was taken every other day and later twice a week and finally discontinued.

Histologic examination of the curettings removed at the time of irradiation showed them to consist of normal endometrium.

COMMENT.—This case was unusual on account of the marked anemia which was present. For this reason operation would have been associated with a definitely increased surgical risk. Prior to her admission to the hospital all sorts of uterine styptics, rest in bed, local applications of ice and even packing of the vagina with gauze had been resorted to in an ineffectual effort to check the hemorrhage.

SUMMARY.—Myoma uteri, multiple tumors forming with the uterus a nodular mass the size of a two and one-half or

three months' pregnancy, normal adnexa. Marked anemia and the development and secondary symptoms incident to the loss of blood. Dilatation and curettage followed by irradiation (1200 mg.h.). Complete amenorrhea, and shrinkage of the tumor. Microscopic examination showed normal endometrium.

METRRORRHAGIA TREATED BY IRRADIATION.—This patient was a white woman 49 years of age. She had three children, the youngest of which was 14 years of age. No miscarriages. With the exception of typhoid fever when 20 and influenza seven years ago, the patient had never been severely ill until the development of the present trouble.

Menstrual history appeared at 14, regular 28-day type, four to five day duration, some dysmenorrhea prior to the birth of the first child, none since, three to four pads for the first three days and then a marked diminution in the amount of the flow.

A moderate amount of leukorrhea has been present since the birth of the first child. This is especially noticeable for a day or two following the cessation of the menstrual flow. This is generally white but occasionally yellowish. Never enough to require the wearing of a pad.

Two years ago the patient noticed that the periods were becoming longer and more profuse. This was not a steady increase from month to month but viewed in periods of three or four months has been definitely progressive until the present time. Periods now vary from seven or eight days to two weeks in duration and on one occasion three months ago she bled for three weeks. At present it is impossible for the patient to prognosticate when a period will begin or how long it will continue. Sometimes the bleeding is quite profuse (eight to ten pads daily) and at other times little more than

a slow ooze requiring one or two pads per day. The flow is generally bright red blood and fades off to a prune juice-colored flow followed for a day or two by the before-mentioned leukorrhea. As a result of the bleeding the patient feels weak but recovers rapidly during the intervals of freedom from hemorrhage. Of late these intervals have been becoming shorter and the headaches, malaise and loss of strength have been becoming more marked.

During the last two years this patient has had three D. and C.'s performed. Each of these operations gave temporary relief but in each case recurrence of the hemorrhage occurred within three to four months. The patient has been referred for hysterectomy. Physical examination reveals a moderately well-nourished woman, appetite good, bowels regular, sleeps well. She is five feet, six inches, weight 128 pounds and gives a history of a loss of five pounds during the last year. Heart and lungs are normal. Urine analysis shows normal urine. Systolic blood pressure 130, diastolic 95. Hemoglobin 40, R.B.C. 4,500,000, W.B.C. 5000. Abdominal examination is negative.

PELVIC EXAMINATION.—External genitalia normal, outlet multiparous, vagina multiparous but there is good support in both anterior and posterior wall. Cervix shows a slight bilateral laceration and erosion, but is otherwise normal, the fundus is normal in size, shape, position, mobility and consistency, the tubes are not palpable, the ovaries can, however, be felt and are normal.

DIAGNOSIS.—Metrorrhagia myopathica, normal adnexa, anemia incident to the pathologic bleeding.

Recommendation D. and C. and irradiation (1200 mg.h.)

OPERATION.—Nitrous oxide gas anesthesia—D. and C. The uterus was normal in depth. Two capsules containing

25 mg. each of properly screened radium laid side by side were introduced in a rubber tube to the fundus and stitched in place. As a preliminary to the D. and C. the area of erosion on the cervix was cauterized. A light gauze vaginal pack was introduced.

Convalescence was entirely normal. The radium was removed at the end of 24 hours, the patient was allowed out of bed on the third day and returned home on the fifth.

Histologic diagnosis of curetings showed normal endometrium.

POSTOPERATIVE HISTORY.—There was permanent amenorrhea. Three months after operation the artificial menopause developed. These were mild and of no greater severity or duration than occur at the normal menopause. The leukorrhea was increased for six weeks following the operation probably due to the cauterization of the cervix. It then ceased. There was a gradual return to health and strength. Three months after the operation the hemoglobin was normal and the headaches and other symptoms incident to the anemia had disappeared. Pelvic examination showed an excellent cervical result and the fundus and adnexa were normal. One year after the operation there were no symptoms, pelvic examination showed normal genitalia, there was no leukorrhea nor had there been any recurrence of bleeding or other illness. The patient has gained 15 pounds in weight and feels in perfect health.

SUMMARY.—This was an uncomplicated case of metrorrhagia probably due to ovarian malfunction. Twelve hundred milligram hours of radium irradiation produced a permanent amenorrhea and cure of all symptoms.

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CHAPTER IX

CERVICITIS

CERVICITIS.—Inflammation of the cervix is the most frequent gynecologic disease. The condition was formerly confused with corporeal endometritis. With the exception of the tuberculous variety chronic corporeal endometritis is a relatively infrequent disease. As a result of this mistaken conception many patients suffering from cervicitis were needlessly submitted to curettage and other intrauterine procedures which failed to benefit their condition and was often actually harmful. Among ill-informed surgeons lack of knowledge upon this point is still common.

Cervicitis may result from infection by various micro-organisms.

GONORRHEA.—This is a frequent type of infection. In the nulliparous woman in whom defloration is present the gonococcus is undoubtedly the most common cause for cervicitis. The urethra and Bartholin's glands are also often infected. During the acute stage the gonococcus is easily demonstrated by staining methods but during the chronic stage the demonstration of the organisms is much more difficult. The Gram stain should be routinely employed and the intracellular location of the organism is essential. One or two negative smear examinations by no means exclude the possibility of gonorrhea being present.

NON-SPECIFIC CERVICITIS.—Among young nulliparous women a non-specific form of cervicitis is by no means uncommon. It is especially likely to occur in hypoplastic uteri with long conical cervixes in which drainage is poor and

is often seen in patients suffering from dysmenorrhea or sterility. Dilatation of the cervical canal generally cures the condition by permitting better drainage. Whereas irradiation would doubtless effect a cure in these cases it is unnecessary. Leukorrhea is rarely a prominent symptom.

Tuberculosis of the cervix is a rare form of cervicitis and is often associated with involvement of the fallopian tubes, pelvic peritoneum and corporeal endometrium and is practically always secondary to a primary focus elsewhere. Tuberculosis of the cervix often simulates carcinoma. We know of one case which was treated by irradiation with 2400 mg.h. of radium under this mistaken diagnosis without benefit. In selected cases operation is the treatment of choice. There is no reason to believe that irradiation has any place in the treatment of cervical tuberculosis.

LACERATIONS OF THE CERVIX.—Major degrees of laceration, especially when associated with marked hypertrophy or eversion are best treated by operation. Minor degrees of laceration frequently cause annoying leukorrhea and often are intractable to local applications. It is in these cases particularly, when unassociated with lacerations of the vagina, or other lesion requiring operative repair, that irradiation may be employed with advantage. These lesions are often spoken of as erosions, and whereas microscopic erosions are generally present, the condition is actually an eversion with subsequent infection and hypertrophy of the exposed mucosa, rather than an actual loss of tissue such as is inferred by the former term. Colon bacilli, staphylococci, varied anaërobes and diphtheroid bacilli have been found present in these cases by Curtis.¹ Lacerations of the cervix associated with gonococcal infection constitute one of the most frequent and intractable forms of cervicitis.

SYMPTOMS OF CERVICITIS.—The most pronounced and often the only symptoms produced by cervicitis is leukorrhea. This is usually a thick tenacious discharge, varying from a glairy white of egg-like material to a yellow or creamy purulent material. Most commonly it is a whitish opaque secretion composed of mucus, epithelial débris and leukocytes. The leukorrhea is generally most profuse after menstruation, next before the period and usually diminishes during the interval stage. Patients vary markedly in their reaction to leukorrhea, some complaining severely on an amount of discharge which is hardly noticed by others. Furthermore, the appearance of the gross lesion is by no means a trustworthy guide as to the amount of leukorrhea which it may produce. Badly lacerated or infected cervixes almost always cause considerable discharge, but not infrequently cervixes, which to palpation and inspection through a speculum appear but slightly lacerated or infected, are the cause of a considerable leukorrhea.

Among hypersensitive patients annoyance is frequently noticeable after the first pregnancy even when the actual amount of leukorrhea is not great, as these women are prone to compare the amount of leukorrhea to the normal secretion present prior to pregnancy. In many cases the amount of leukorrhea seems to vary with the general health of the patient. With the cessation of the activity of the glandular epithelium following the normal menopause leukorrhea usually ceases. It is possible that cervicitis may occasionally be the focus for metastatic infections, but in our experience this has rarely been demonstrable. Metastatic gonococcal infections occur but are less frequent in women than in men and when present other areas in the genital tract besides the cervix are usually infected. The old idea that lacerations of

the cervix caused a long train of more or less vague and variable symptoms is erroneous.

We do not mean to infer that the cervix is never a cause of metastatic infection but merely that in our experience this has been infrequent and that other possible sources such as the tonsils, teeth, etc., should be examined first when attempting to demonstrate a primary focus. Cervicitis, especially when associated with lacerations, is a definite predisposing factor towards the occurrence of carcinoma and for this reason, if for no other, calls for eradication. It is probable that it is the infection incident to the laceration and not the tear itself that is the predisposing factor.

SELECTION OF CASES.—Irradiation should never be employed during the acute stage of the disease nor in cases suffering from inflammatory lesions of the tubes or ovaries. Severe grades of laceration, especially when associated with much hypertrophy, or when accompanied with laceration of the pelvic floor, or other lesions requiring operation, are best treated by some form of plastic operation—trachelorrhaphy, trachelectomy or the Sturmdorff operation. For office work the cautery often gives good results in cases of minor grade lacerations. There are, however, some cases in which none of these methods of treatment seems advisable and for these irradiation may be employed. It must be emphasized that leukorrhea is the only symptom which can be cured by the irradiation and that only small doses can be safely employed in patients during the active menstrual life. Cervicitis occurs during the child-bearing period and the production of the irradiation menopause by the cervical application of radium is entirely possible, unless a small standard of dosages is rigidly adhered to. The authors' experience with irradiation for cervicitis is limited to a small

series of cases which have not been adequately followed up. Distinct benefit followed the treatment in many cases, and in none were harmful effects noticed.

To Curtis² belongs the credit for introducing the treatment of cervicitis by irradiation and his technique has been followed by us and is as follows: Under nitrous oxide anesthesia, the cervical canal is investigated with graduated dilator. Thorough dilatation is accomplished without producing laceration. Diagnostic curettage, separate for cervix and fundus, may be desired. Two 25 mg. tubes of properly screened radium are introduced into the cervix and held in place by a stitch clamped with a hemostat as described under the treatment of benign hemorrhage. Young women receive 250 to 350 mg.h. Curtis³ allows the radium to remain in place five to seven hours; treatment by this dosage does not disturb normal menstruation. Patients over 35 years of age must be treated with smaller doses. We cannot do better than quote Curtis regarding the effect. He states that the immediate result of radium treatment is increased discharge which persists for many weeks. This stage is often followed by a stationary period of a month or two. Meantime the cervix should be dilated occasionally at the office to prevent cervical stenosis.

Gradual improvement is the rule, but a considerable number require a second irradiation to effect a cure. This is preferably postponed for several months, first, because one treatment may eventually prove sufficient, second because it is desired to ascertain with certainty that the irradiation has not interfered with the menstrual function. If a second irradiation is required the dosage is slightly reduced. Curtis states that it should be especially emphasized that he has observed several patients with long standing leukorrhea, in

whom the result of irradiation appeared unsatisfactory, but who nine months or a year later showed complete recovery from their affliction. Curtis also emphasized the importance of the eradication of the infection from Skene's ducts and other local areas of contamination. By this means he has cured leukorrhea in 87 per cent. of 104 patients.

The beneficial action of irradiation in cases of cervicitis is probably due to the production of fibrous tissue with the resulting contraction. It is doubtful if in the dosage employed any marked action upon the glandular epithelium occurs. Glandular atrophy undoubtedly takes place but is probably secondary to the connective tissue formation.

MEMBRANOUS DYSMENORRHEA.—This is a form of dysmenorrhea in which the superficial layers of the endometrium are cast off at each menstrual period. In the most typical cases a complete cast of endometrium is expelled, in others this cast is passed in broken up particles varying in size but generally easily discernible to the naked eye. The disease may manifest itself with puberty or may develop in later life. It is frequently associated with sterility and may probably be a factor in the production of the latter condition. Cures have, however, been recorded in multiparas in whom the disease has been present prior to conception. It is more common in ill-nourished anemic patients.

It was formerly thought that membranous dysmenorrhea was a form of endometritis. Its frequency in virginal individuals and more careful histologic and bacteriologic investigations have disproved this assumption. Careful bacteriologic examination of the endometrium in these cases has shown it to be sterile (Ascheim⁴). Halban⁵ believes this condition due to hyperfunction of the ovaries resulting in premature uterine contractions which produce separation of the

endometrium. On this assumption, and the strength of a suggestion by Dr. George Gray Ward who had treated a case by irradiation with favorable results, one of the authors began the treatment of a small series of cases by means of radium.

Seven cases have been treated, four were cured when last heard from two or more years after irradiation. One case was well for nine months when there was a return of the condition, a second irradiation was performed and the patient has been well for sixteen months since. One other case treated two years ago is much benefited. The seventh case had amenorrhea for three months following the treatment, then a period of five months of normal flow followed by a recurrence of symptoms. No ill effects followed any of the treatments. Whereas this series is too small from which to draw definite conclusions, it would seem that irradiation for this disease is worthy of a more extensive trial especially as other forms of treatment are by no means uniformly satisfactory. The above cases were treated by an ordinary dilatation and curettage. The technique of irradiation was the same as that employed in the treatment of benign hemorrhages except that the dosage was reduced to 250 or 350 mg.h.

PSUEDOMYXOMA PERITONEI.—This condition is the result of the escape into the peritoneal cavity of pseudomucus- and pseudomucin-producing cells. The common cause is the intraperitoneal rupture of a pseudomucinous cyst of the ovary. A number of cases have been recorded following the rupture of a mucocele of the vermiform appendix and in the male this is the most frequent etiologic factor. The pseudomucei-producing cells become implanted on the peritoneum in much the same manner as carcinoma may be implanted under similar circumstances. The development of the lesions

is, however, slower. In this way papillomatous-like masses of various sizes may develop on any of the serous surfaces. Numerous adhesions are found and the clinical picture closely simulates carcinomatosis of the peritoneum except that the evolution of symptoms is slower. Many cases ultimately undergo malignant changes. Estimates as high as 50 per cent. have been recorded. The disease is essentially a surgical one. The author has seen one case, however, which was hopelessly inoperable. This case was treated by X-ray with such marked improvement that three months later operation was successfully performed. This patient, although 72 years of age, is well and without any evidence of disease at the present date—18 months later. There was no doubt as to the benefit secured by the X-ray treatments in this case and postoperative X-ray would, therefore, seem an added safeguard in these cases. If, at operation, it is found impossible to remove all the new-growths, implantation of bare tubes is worthy of a trial. This is doubly the case if the tumors appear to be undergoing malignant degeneration.

GRANULOMA INGUINALÆ.—This disease is comparatively infrequent in temperate zones. Its similarity to syphilitic lesions and carcinoma and to a somewhat lesser extent to tuberculosis and chancroids requires careful exclusion by laboratory methods. The disease is usually treated by the administration of tartar emetic. More recently, Randall⁶ has successfully employed sodium antimony thioglycolate and the triamid of antimony thioglycolic acid. One moderately early case was treated by one of the authors with bare tubes. No other treatment was employed except cleanliness and a dusting powder of boric acid. As soon as the primary reaction disappeared healing commenced and the ulcer which originally was eight cm. in diameter entirely disappeared in eight

weeks. There was no recurrence one year later. Care must be exerted not to produce undue scar formation. Whereas little can be deducted from the treatment of one case it would appear that a further trial of this method is justifiable in selected cases or in those which do not yield to the ordinary methods. The favorable result secured in the aforementioned case was more rapid than generally attained with the tartar emetic treatment.

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CHAPTER X

STERILITY AND DYSMENORRHEA

MALIGNANT OVARIAN TUMORS

THE TREATMENT OF STERILITY AND DYSMENORRHEA BY IRRADIATION.—Differentiation must be made between a sterile marriage and a sterile woman. The male partner is defective in from 40 to 50 per cent. of sterile marriages. It is obviously useless to treat the woman if the male partner is at fault. Sterility is a symptom and not a disease and may be the result of a variety of causes. Although sterility may be the only symptom present it is nevertheless essential that each case be studied individually and an effort made to determine the etiologic factors present in the particular case. It is patently useless to perform dilatation of the cervical canal in a case in which the tubes are occluded.

Certain cases of sterility and dysmenorrhea are apparently due to hypofunction of the ovaries. These cases are often associated with hypoplasia of the uterus and a shallow vaginal lake. Such ovaries are of the infantile type, long, flat organs and possess few or no developing follicles. Clinically the uteri in these cases possess long, narrow, snout-like cervixes which often project deeply into the vagina, the external os is small and pin point. The body of the uterus is small and acutely antiflexed. The cervical canal is equal or sometimes twice the length of this cavity of uterus measured from the internal os. The menstrual history is that of primary dysmenorrhea, the flow is scant and of short duration. The intervals between the periods is often prolonged and irregu-

lar. The dysmenorrhea is prone to develop before the onset of the flow, often beginning a day or two before the appearance of the flow and in other cases a few hours prior to the onset. The pain is of a dull aching character and is situated over the uterus, lower lumbar and sacral regions. In some instances, the pain is distinctly ovarian in location.

Cases of hypoplasia are by no means uncommon and are essentially the type in which stimulation by irradiation may be of value. It has long been recognized that mild irradiation by means of X-ray or radium stimulates the development of certain seeds. Seeds thus treated grow more rapidly and produce larger plants and blooms. Unless especial precautions are adopted women workers with radium or X-ray frequently develop menstrual irregularities. These are usually of the menorrhagic type. If the exposures are persisted in, scant and irregular menstruation develops and finally complete amenorrhea. These workers are probably exposed only to extremely slight effects of the radium or X-ray and the fact that most of them develop a menorrhagia until the prolonged effects of the rays begin to produce an inhibitory effect upon the ovaries should be emphasized. The latter fact has been noted by Simpson¹ and others. Bearing these facts in mind as well as being influenced by the efforts of others along this line, Rubin treated a series of cases with small doses of X-ray. Of 12 cases treated by Rubin² with mild doses of X-ray, pregnancy resulted in nine—one aborted. X-ray treatment resulted in restitution of the menses in all of 12 cases of amenorrhea.

Irradiation for amenorrhea was employed by Van de Velde³ and Flatau⁴ and others. Flatau irradiated 38 cases and reported good results in 25. Martius,⁵ Recasens, Seitz, Mansfeld, Schonhof, Meiner, Goedel, Van de Velde and

Flatau confirm the excellent results secured by irradiation in such cases. Rongy⁶ reported 13 cases of amenorrhea treated, in five of whom menstruation was reëstablished.

Hirsch⁷ also reports the use of irradiation for the treatment of hypofunction of the ovary and concludes that the results of irradiation treatment in carefully selected cases is capable of producing improvement in ovarian function as shown by regulation of the menstruation and the induction of pregnancy with birth of healthy children. Hirsch employs 15 per cent. of the castration dose delivered to each ovary. The irradiation should not be repeated until after a lapse of several months but meanwhile a small dose of irradiation may be applied to the thyroid and hypophyses if the state of the patient demands it. Hirsch recommends a slight variation from the 15 per cent. dosage depending upon the age, thickness of the abdominal wall and duration of the ovarian hypofunction. Rubin gave on an average of 10 per cent. of the E. S. D. to his cases.

Irradiation treatment either for sterility or scanty menstruation should be employed cautiously and, although good results have been recorded, the treatment is by no means standardized. The dangers of the treatment are obvious and in the case of amenorrhea, other causes such as anemia, pulmonary tuberculosis and conditions other than hypofunction of the ovary should be carefully excluded prior to irradiation. Irradiation by means of an intrauterine application of radium possesses some advantages over the X-ray. In the case of sterility, a Rubin's test should be performed at the same sitting as it is useless to stimulate the ovary if the tubes are not patent. The advantages of a thorough examination under an anesthetic and the benefits of a cervical dilatation should also be taken into account. The possibility

of producing a permanent amenorrhea where perhaps only a temporary one was present should also be considered and for this reason the treatment should not be attempted except by one familiar with gynecologic irradiation and diagnosis. Furthermore, the treatment should not be repeated unless results as indicated by an improved ovarian function are secured and in no case should there be a repetition of the treatment for several months. The authors have had only a limited experience with the treatment of irradiation for ovarian hypofunction but would hesitate to repeat the treatment in less than five months as a minimum and believe that a longer interval would be safer in the average case.

Our technique has been to anesthetize and prepare as for an ordinary plastic operation. The Ruben's test is then performed followed by a thorough dilatation of the cervix and curettage. Fifty mg.h. of properly screened radium encased in a rubber tube is inserted to the fundus and held in place by the same technique as described under the treatment of benign hemorrhage. Between 200 and 300 mg.h. are given according to the age of the patient.

Nine cases apparently suffering from hypofunction of the ovaries have been treated; none has been treated for more than nine months.

In five of these cases sterility was the chief feature and four were treated for dysmenorrhea. No pregnancy has resulted although the time elapsed since the treatment is in some instances quite short. Of the nine cases all of whom suffered from dysmenorrhea and scanty and in some cases infrequent menstruation, there has been no improvement in four, in two there has been slight improvement in the character of menstruation and three have been markedly improved. In none has a second irradiation been performed. The time

which has elapsed since the treatment of these cases is still too short to form any conclusion regarding the permanency of the improvement in those cases which have been benefited — indeed our series is too small and too recent from which to draw any adequate conclusions, and it must be borne in mind that the thorough dilatation to which all have been submitted may account for some of the benefit derived.

However, there would seem to have been enough benefit accrued to warrant a further trial of this method. For example, one of our sterility cases was a woman 35 years of age who had always suffered from dysmenorrhea and scanty menstruation, the periods lasting only one or two days and averaging in periodicity from 30 to 90 days. This patient's chief symptom was sterility. She had been treated by a number of competent gynecologists and had had three dilatation operations performed without benefit. Since an irradiation of 200 mg.h. four months ago she has had three periods, each of which has lasted four days with a marked increase in the amount of the flow. The general condition of this patient is good, and there seems at least a chance that pregnancy may occur. The patient herself is very much encouraged and states that the periods have never been so normal as since the treatments.

MALIGNANT OVARIAN NEOPLASMS.—Various types of malignant tumors occur in the ovary. About 15 per cent. of all ovarian tumors are malignant. Ovarian tumors may be malignant from the beginning or benign neoplasms may undergo a malignant degeneration. Pseudomucinous cysts are particularly prone to develop areas of carcinoma. Many malignant tumors are bilateral but this tendency is especially noticeable among those which are primarily malignant. The prognosis is somewhat more favorable in the secondary form

for, in this variety, the malignant area may develop in the centre of a benign tumor and be entirely encapsulated. Bilateral tumors, adhesions, the presence of areas of malignant new-growths upon the outer surfaces, and rupture are unfavorable signs. Glandular adenocarcinoma is nearly twice as malignant as the papillary form. Rapidity of growth, the development of ascites, the bilateral character of the tumor, anemia and cachexia all suggest a malignant rather than a benign tumor. During the early stage, subjective symptoms are often mild and, in fact, the general silent character of the disease is rather characteristic.

The treatment of all malignant ovarian neoplasms is essentially surgical. As long as there is any hope that the tumor can be removed, operation is indicative. Operation is advisable if there is any doubt whatever as to the malignant character of the disease. Operation may be advisable as a merely palliative procedure and, finally, in many cases in which ascites is present, a small exploratory incision, perhaps performed under local anesthesia, is preferable to paracentesis abdominalis. As a general rule, therefore, even if it is merely an exploratory incision or for temporary relief of ascites, operation should be performed. A piece of tissue should invariably be removed for microscopic examination. The discomfort and mortality under such circumstances is small, and, in many cases, the procedure offers the only means of positively establishing the diagnosis. In every large series there will occasionally be found a benign lesion which is curable and which has simulated malignancy so closely that prior to operation it will have been thought positively hopeless. During the last year three such cases have been encountered in the Gynecological Department of the University Hospital. One of these, an especially interesting case

of pseudomyxoma of the peritoneum presented all the clinical manifestations of a general peritoneal carcinomatosis of ovarian origin, and had been so diagnosed and operation refused by two competent surgeons. In this case, even after the abdomen was opened, the diagnosis of malignancy appeared confirmed. As a result of the histologic examination of the tissue the true character of the lesion was established and a second operation performed which resulted in the cure of the patient.

The value of preoperative irradiation either by means of radium or X-ray is probably more than counterbalanced by the loss of time entailed and is, therefore, not recommended. A routine postoperative irradiation by deep X-ray will probably result in slightly raising the proportion of cases alive at the end of five years. Deep X-ray therapy for recurrences occasionally results in cure, or, at least, prolonging life and relieving symptoms. For extensive recurrences with widespread peritoneal involvement X-ray therapy is useless.

The lead treatment as suggested by Blair-Bell, may ultimately prove of value in these cases. Five cases from the series of one of the authors at the Philadelphia General Hospital have received the lead treatment. Two died within one month, one died three months later without any apparent benefit, one case is alive and shows little change one month after the initial treatment and one case shows subsidence of the lesion five months later. The two latter cases received X-ray therapy in addition to the lead.

Until three years ago, the authors were of the belief that irradiation therapy was useless in the treatment of malignant ovarian tumors. Prior to that time, thirteen cases in which incomplete operations had been necessary were submitted to postoperative X-ray without benefit. A case was then seen

in which one of us had performed a panhysterectomy and bilateral salpingo-oöphorectomy for moderately advanced bilateral cystic adenocarcinoma. Fifteen months after the operation bilateral tumors were present, one the size of the fetal head at term and the other only slightly smaller, both were densely adherent and surgical removal was out of the question. As a last hope deep X-ray therapy was instituted and carried out by Pancoast at the University Hospital. The tumors almost immediately began to shrink and at the present time, 22 months after the first X-ray treatment, no trace of neoplasm is demonstrable, the patient has more than regained her normal weight, and is entirely free of symptoms.

Since the occurrence of this case a routine course of postoperative deep X-ray therapy has been advised for all cases. Three additional cases in which recurrence had developed following operation have been given this treatment. In two, the disease continued to advance and death resulted, the third is free of symptoms, has regained her normal weight, and no evidence of the recurrence is demonstrable nine months after the first X-ray treatment. It is as a result of the favorable results secured in these two cases that has lead us to recommend deep X-ray therapy as a routine postoperative measure and to employ the treatment in all postoperative recurrences except those that are absolutely hopeless. The postoperative course of deep X-ray therapy is begun as soon as complete healing of the abdominal wound has occurred, usually two or three weeks after operation. Our experience is that the average malignant ovarian neoplasm is unaffected by the X-ray but that occasionally a tumor is encountered which is particularly susceptible, and that this form of postoperative treatment is, therefore, worthy of further trial.

Healy,⁸ in his discussion of a paper by one of the authors, stated that at the Memorial Hospital a small percentage of cases of known ovarian malignancy had been markedly benefited by this form of treatment and that a few had survived a three-year period.

Pribram,⁹ in recording the end-results in a series of 95 malignant ovarian tumors, states that he has never seen a cure result from X-ray treatment, but that in advanced cases temporary improvement and prolongation of life may sometimes result, and in border-line cases which have been submitted to radical operation, the dangers of recurrences may be decreased. Zweifel states that he has never seen a case cured by either X-ray or radium.

As already stated and despite the well-recognized facts that X-ray therapy is time-consuming and sometimes followed by more or less discomfort we have seen an occasional case so benefited that we believe the treatment worthy of a further trial in the type of cases already specified. The X-ray is only recommended after the utmost has been done to eradicate the disease by surgical measures. The X-ray work should be correlated with a careful histologic study of each tumor in an effort to determine its relative efficiency in the different types of malignant neoplasms. The results of the X-ray treatment should be checked by a competent surgeon and should be given by an experienced Roentgenologist.

ADENOMYOMA OF THE RECTOVAGINAL SEPTUM.—On account of their location these lesions are often extremely difficult to treat satisfactorily by surgical measures. One of the authors has recently treated two such cases by the implantation of gold-encased emanation. In both there has been marked improvement and shrinkage of the growths. The method is worthy of a further trial.

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